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Smart KM, Ferraro MC, Wand BM, O'Connell NE

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[Intervention Review]

Physiotherapy for pain and disability in adults with complex regional pain syndrome (CRPS) types I and II

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ABSTRACT

Background

Complex regional pain syndrome (CRPS) is a painful and disabling condition that usually manifests in response to trauma or surgery and is associated with significant pain and disability. CRPS can be classified into two types: type I (CRPS I) in which a specific nerve lesion has not been identified and type II (CRPS II) where there is an identifiable nerve lesion. Guidelines recommend the inclusion of a variety of physiotherapy interventions as part of the multimodal treatment of people with CRPS. This is the first update of the review originally published in Issue 2, 2016.

Objectives

To determine the effectiveness of physiotherapy interventions for treating pain and disability associated with CRPS types I and II in adults.

Search methods

For this update we searched CENTRAL (the Cochrane Library), MEDLINE, Embase, CINAHL, PsycINFO, LILACS, PEDro, Web of Science, DARE and Health Technology Assessments from February 2015 to July 2021 without language restrictions, we searched the reference lists of included studies and we contacted an expert in the field. We also searched additional online sources for unpublished trials and trials in progress.

Selection criteria

We included randomised controlled trials (RCTs) of physiotherapy interventions compared with placebo, no treatment, another intervention or usual care, or other physiotherapy interventions in adults with CRPS I and II. Primary outcomes were pain intensity and disability. Secondary outcomes were composite scores for CRPS symptoms, health-related quality of life (HRQoL), patient global impression of change (PGIC) scales and adverse effects.

Data collection and analysis

Two review authors independently screened database searches for eligibility, extracted data, evaluated risk of bias and assessed the certainty of evidence using the GRADE system.

Main results

We included 16 new trials (600 participants) along with the 18 trials from the original review totalling 34 RCTs (1339 participants). Thirty-three trials included participants with CRPS I and one trial included participants with CRPS II. Included trials compared a diverse range of interventions including physical rehabilitation, electrotherapy modalities, cortically directed rehabilitation, electroacupuncture and exposure-based approaches. Most interventions were tested in small, single trials. Most were at high risk of bias overall (27 trials) and the remainder were at 'unclear' risk of bias (seven trials). For all comparisons and outcomes where we found evidence, we graded the certainty of the evidence as very low, downgraded due to serious study limitations, imprecision and inconsistency. Included trials rarely reported adverse effects.

Physiotherapy compared with minimal care for adults with CRPS I

One trial (135 participants) of multimodal physiotherapy, for which pain data were unavailable, found no between-group differences in pain intensity at 12-month follow-up. Multimodal physiotherapy demonstrated a small between-group improvement in disability at 12 months follow-up compared to an attention control (Impairment Level Sum score, 5 to 50 scale; mean difference (MD) -3.7, 95% confidence interval (CI) -7.13 to -0.27) (very low-certainty evidence). Equivalent data for pain were not available. Details regarding adverse events were not reported.

Physiotherapy compared with minimal care for adults with CRPS II

We did not find any trials of physiotherapy compared with minimal care for adults with CRPS II.

Authors' conclusions

The evidence is very uncertain about the effects of physiotherapy interventions on pain and disability in CRPS. This conclusion is similar to our 2016 review. Large-scale, high-quality RCTs with longer-term follow-up are required to test the effectiveness of physiotherapy-based interventions for treating pain and disability in adults with CRPS I and II.

PLAIN LANGUAGE SUMMARY

Does physiotherapy improve pain and disability in adults with complex regional pain syndrome?

Key messages

We are very uncertain if physiotherapy treatments improve the pain and disability associated with complex regional pain syndrome (CRPS).

We are very uncertain because the clinical trials we found:

- were not conducted or reported as well as they could have been (or both);

- included small numbers of patients with CRPS;

- tested a large range of different types of physiotherapy treatments; and

- because there were a limited number of trials that investigated any particular physiotherapy treatment.

We are very uncertain if physiotherapy treatments cause unwanted side effects; more evidence is required to clarify this.

Good-quality clinical trials are required to further investigate whether or not physiotherapy treatments improve the pain and disability associated with CRPS.

Treating pain and disability in adults with complex regional pain syndrome

Complex regional pain syndrome is a painful and disabling condition that can occur after trauma or surgery and is associated with significant pain and disability. CRPS can be classified into two types: type I (CRPS I) in which a specific nerve injury has not been identified and type II (CRPS II) where there is an identifiable nerve injury. Guidelines recommend that physiotherapy rehabilitation should be included as part of the treatment for CRPS. Physiotherapy for CRPS could include a range of treatments and rehabilitation approaches, such as exercise, pain management, manual therapy, electrotherapy or advice and education, either used alone or in combination. Physiotherapy is recommended because it is thought that it may improve the pain and disability associated with CRPS.

What did we want to find out?

We wanted to find out if physiotherapy treatments improve pain and disability in adults (aged over 18) with CRPS.

What did we do?

We searched for clinical trials that involved adults with CRPS, which compared physiotherapy treatments to placebo treatments or routine care or which compared different physiotherapy treatments to each other.

We compared and summarised the results of the studies and rated our confidence in the evidence, based on factors such as trial methods, size and length of follow-up.

What did we find?

We found 33 clinical trials that involved 1317 people in total with CRPS type I of the upper or lower limb, or both. The trials investigated the effect of a range of physiotherapy treatments. We found only one trial involving 22 people with CRPS type II.

Here we present the findings from comparisons between different physiotherapy treatments and placebo treatments or routine care and for comparisons of different physiotherapy treatments to each other.

Reducing pain

We are uncertain if any of the physiotherapy treatments investigated in the clinical trials we identified help reduce the pain associated with CRPS.

Reducing disability

We are uncertain if any of the physiotherapy treatments investigated in the clinical trials we identified help reduce the disability associated with CRPS.

Side effects

We are uncertain if any of the physiotherapy treatments investigated in the clinical trials we identified cause any unwanted side effects.

What are the limitations of the evidence?

Clinical trials were small and most have been conducted in ways that could introduce errors into their results. This limited our confidence in the evidence.

How up to date is the evidence?

The evidence is up to date to July 2021.

SUMMARY OF FINDINGS

Summary of findings 1. Physiotherapy compared with minimal care for adults with CRPS I

Physiotherapy compared with minimal care for adults with CRPS I

Patient or population: adults with CRPS I

Settings: outpatient clinic

Intervention: multimodal physiotherapy

Comparison: 'social work' (i.e. passive attention, advice)

Outcomes	Effect size (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
Oerlemans 1999 Pain (VAS 0 to 100)	Not estimable	—	—	—
Oerlemans 1999 Disability as measured by the impairment level sum score (5 to 50) Higher scores indicate greater impairment Measured 12 months post recruitment	MD -3.7 95% CI -7.13 to 0.27	91 (1)	⊕⊖⊖⊖ **very low**[a,b,c]	One study found evidence of a small beneficial effect of physiotherapy compared to 'social work' (i.e. an attention and advice control) intervention
Incidence/nature of adverse effects	Not estimable	—	—	Data not reported

CI: confidence interval; **CRPS I:** complex regional pain syndrome type I; **MD:** mean difference; **VAS:** visual analogue scale

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect;
Very low certainty: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded once for serious study limitations.
[b]Downgraded once for inconsistency.
[c]Downgraded once for imprecision.

Summary of findings 2. Physiotherapy compared with minimal care for adults with CRPS II

Physiotherapy compared with minimal care for adults with CRPS II

Patient or population: adults with CRPS II

Settings: any

Intervention: multimodal physiotherapy

Comparison: any eligible comparison

Outcomes	Effect size (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
Pain (VAS 0 to 100)	No data	—	—	—
Disability	No data	—	—	—
Incidence/nature of adverse effects	No data	—	—	—
CRPS II: complex regional pain syndrome type II				

CI: confidence interval; **CRPS:** complex regional pain syndrome; **VAS:** visual analogue scale

BACKGROUND

This is the first update of a review of physiotherapy interventions for complex regional pain syndrome originally published in 2016 (Smart 2016).

Description of the condition

Complex regional pain syndrome (CRPS) is a persistent, painful and disabling condition that usually, but not exclusively, manifests in response to acute trauma or surgery (Goebel 2011; Shipton 2009). The International Association for the Study of Pain (IASP) introduced the diagnostic label 'CRPS' in the 1990s in order to standardise inconsistencies in terminology and diagnostic criteria (Merskey 1994). Two sub-categories of CRPS have been described: CRPS type I (CRPS I) (formerly and variously referred to as reflex sympathetic dystrophy (RSD), algodystrophy, Sudek's atrophy), in which there is no clear evidence of a nerve lesion and CRPS type II (CRPS II) (formerly referred to as causalgia, algoneurodystrophy), in which a co-existing nerve lesion (as determined by nerve conduction studies or surgical inspection, for example) is present (Coderre 2011; Todorova 2013).

CRPS is characterised by symptoms and signs typically confined to a body region or limb, but which may become more widespread (van Rijn 2011). The diagnostic criteria for CRPS originally proposed by Veldman et al (Veldman 1993) and subsequently by the IASP (Merskey 1994) have since been revised in response to their low specificity and potential to over-diagnose cases of CRPS. The Budapest criteria proposed by Harden 2010 have enhanced diagnostic accuracy and are now widely accepted (Goebel 2011). The diagnosis of CRPS is clinical and the cardinal features include (Goebel 2011):

1. continuing pain disproportionate to any inciting event;
2. the presence of clusters of various symptoms and signs reflecting sensory (e.g. hyperaesthesia, allodynia), vasomotor (e.g. asymmetries of temperature or skin colour, or both), sudomotor (e.g. oedema or altered sweating or both), motor (e.g. reduced range of motion, tremor) or trophic (e.g. altered hair or nails, or both) disturbances; and
3. the absence of any other medical diagnosis that might better account for an individual's symptoms and signs.

However, a recent international survey of clinical practice found half of health professionals who provided clinical care to patients with CRPS had difficulty in recognising the symptoms of CRPS (Grieve 2019). Symptom profiles can vary between individuals with CRPS (Borchers 2014) and while statistically determined phenotypes (‘central’, ‘peripheral’ and ‘mixed’ phenotypes) have been suggested (Dimova 2020), their clinical significance is as yet unclear.

The pathophysiological mechanisms underlying CRPS are not fully understood (Harden 2010). Current understanding implicates multiple mechanisms including complex contributions from a maladaptive pro-inflammatory response and a disturbance in sympathetically mediated vasomotor control, together with maladaptive peripheral and central neuronal plasticity (Birklein 2017; Bruehl 2010; Bruehl 2015; Knudsen 2019; Marinus 2011; Parkitny 2013). Furthermore, mechanisms, and in consequence symptoms and signs, may vary between individuals and within individuals over the time course of the disorder, thus heightening the complexity (Marinus 2011).

The incidence of CRPS is not accurately known but population estimates indicate an incidence of somewhere between five and 26 cases per 100,000 person-years (Marinus 2011). A likely conservative 11-year period prevalence rate for CRPS of 20.57 per 100,000 people has been reported (Sandroni 2003). CRPS is three to four times more likely to occur in women than in men, and although it may occur at any time throughout the lifespan, it tends to occur more frequently with increasing age (Shipton 2009). Genetic susceptibility may serve as an aetiological risk factor for the development of CRPS (de Rooij 2009). In individuals who develop CRPS after a fracture, intra-articular fracture, fracture-dislocation, pre-existing rheumatoid arthritis, pre-existing musculoskeletal co-morbidities (e.g. low-back pain, arthrosis) (Beerthuizen 2012) and limb immobilisation (Marinus 2011) may increase the risk of its development. A retrospective analysis of risk factors for the development of CRPS I in a large (22,533 patients) 'Nationwide Inpatient Sample' database from 2007 to 2011 in the United States found female gender, Caucasian race, higher median household income, depression, headache and drug abuse to be associated with a higher rate of CRPS I in an inpatient population (Elsharydah 2017). Others have found that psychological traits, such as depression, anxiety, neuroticism and anger, have so far been discounted as risk factors for the development of CRPS (Beerthuizen 2009: Lohnberg 2013), although further prospective studies are required to substantiate this assertion (Harden 2013). However, they may be associated with poorer outcomes once the condition has developed (Bean 2015). Studies into the course of CRPS present contradictory findings. Whilst some studies have reported complete and partial symptom resolution within one year (Sandroni 2003; Zyluk 1998), other studies have indicated more protracted symptoms and impairments lasting from three to nine years (de Mos 2009; Geertzen 1998; Vaneker 2006). Evidence from prognostic studies of CRPS is scarce and contradictory (Wertli 2013).

People with CRPS have been found to have poor knowledge of the condition (Brunner 2010), and experience significant suffering and disability (Bruehl 2010; Lohnberg 2013). It appears that men with CRPS are more likely to experience depression and kinesiophobia and use more passive coping strategies than women (van Velzen 2019). Preliminary data suggest that interference with activities of daily living, sleep, work and recreation is common and further contributes to a diminished quality of life (Galer 2000; Geertzen 1998; Kemler 2000; Sharma 2009). Qualitative data concerning the lived experience of CRPS from the patient's perspective is emerging. Such studies have found that living with CRPS is a daily battle, and that coping with changing symptoms together with the knowledge that there is no known cure can be particularly challenging (Johnston-Devin 2018). Furthermore, living with CRPS can have a widespread impact on personal and social relationships and intimacy (Packham 2020). Another qualitative study that investigated the informational needs of people living with CRPS found patients wanted honest and accurate information, the opportunity to meet others with the condition and readily available resources with which to facilitate access to local expertise (Grieve 2016a).

Guidelines for the treatment of CRPS recommend an interdisciplinary multimodal approach, comprising

pharmacological and interventional pain management strategies together with rehabilitation, psychological therapy and educational strategies (Goebel 2018; Harden 2013; Perez 2010; Stanton-Hicks 2002), and two international surveys of clinical practice suggest such care is being delivered (Grieve 2019; Miller 2017). However determining the optimal approach to therapy remains clinically challenging (Cossins 2013; O'Connell 2013; Shim 2019).

Description of the intervention

Despite the fact that their effectiveness is not known, guidelines recommend the inclusion of a variety of physiotherapy interventions as part of the multimodal treatment of CRPS (Goebel 2018; Perez 2010; Stanton-Hicks 2002). Physiotherapy has been defined as "the treatment of disorders with physical agents and methods" (Anderson 2002). For CRPS this could include any of the following interventions employed either as stand-alone interventions or in combination: manual therapy (e.g. mobilisation, manipulation, massage, desensitisation); therapeutic exercise and progressive loading regimens (including hydrotherapy); electrotherapy (e.g. transcutaneous electrical nerve stimulation (TENS), therapeutic ultrasound, interferential, shortwave diathermy, laser); physiotherapist-administered education (e.g. pain neuroscience education); as well as cortically directed sensory-motor rehabilitation strategies (e.g. graded motor imagery (GMI), mirror therapy, sensory-motor retuning, tactile discrimination training).

How the intervention might work

The precise mechanisms of action through which various physiotherapy interventions are purported to relieve the pain and disability associated with CRPS are not fully understood. Theories underpinning the use of manual therapies to relieve pain include the induction of peripheral or central nervous system-mediated analgesia, or both (Bialosky 2018). While therapeutic exercise may bring about exercise-induced analgesia by positively influencing i) central pain processing, via endorphin-mediated inhibition for example (Nijs 2012), ii) immune system function and iii) the affective aspects of pain (Smith 2019), and improve function, and by extension disability, by restoring range of movement at affected joints and improving neuromuscular function and load tolerance (Kisner 2002). Theories underlying the use of electrotherapy modalities, also known as electrophysical agents, for pain relief variously include spinal cord-mediated electro-analgesia, heat- or cold-mediated analgesia and anti-inflammatory effects (Atamaz 2012; Logan 2017; Robertson 2006). Pain neuroscience education aims to reduce pain and disability by helping individuals to better understand the biological processes underlying their pain in a way that positively changes pain perceptions and attitudes (Moseley 2015). Other rehabilitation strategies, such GMI or mirror therapy, may provide pain relief or increase mobility, or both, by ameliorating maladaptive somatosensory and motor cortex reorganisation (Moseley 2012).

Why it is important to do this review

A number of systematic reviews suggest that physiotherapy interventions (e.g. exercise, GMI, TENS) employed in combination with medical management may be beneficial in reducing the pain and disability associated with CRPS (Daly 2009; Smith 2005). However, the inclusion of non-randomised clinical trials and case series designs, together with the exclusion of studies involving people with CRPS II as well as those published in a language other than English, may have biased these conclusions. Given the limitations of existing systematic reviews, together with the availability of potentially numerous physiotherapy treatment strategies for CRPS, an up-to-date systematic review of the evidence from randomised clinical trials for the effectiveness of these interventions may assist clinicians in their treatment choices and inform future clinical guidelines that may be of use to policymakers and those who commission healthcare for people with CRPS.

Our original Cochrane systematic review of physiotherapy interventions for CRPS found very low-quality evidence supporting the use of graded motor imagery and mirror therapy for pain and disability in people with CRPS I while evidence of the effectiveness of most other physiotherapeutic interventions was generally absent or unclear. Additionally, we found no eligible trials of physiotherapy interventions for CRPS II (Smart 2016). An update to our original Cochrane systematic review of physiotherapy interventions for CRPS was considered appropriate given the publication of a number of additional clinical trials since the endpoint of our original search (February 2015).

OBJECTIVES

To determine the effectiveness of physiotherapy interventions for treating pain and disability associated with CRPS types I and II.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) (including those of parallel, cluster-randomised and cross-over design) published in any language. Translators identified by the Managing Editor of the Cochrane Pain, Palliative and Supportive Care Group evaluated studies published in a language other than English. We excluded studies in which participants were not randomised to intervention groups.

While we accept that non-randomised studies (e.g. case series, quasi-experimental designs) can provide “proof of concept”-level evidence for healthcare interventions it is our contention that such evidence should not be used to inform clinical treatment decision-making because such evidence is less robust and subject to greater risks of bias than RCTs (Shea 2017). Also, given that our original systematic review identified 18 clinical trials we decided there was no justification for including non-randomised studies on the grounds of an absence of RCT data upon which to inform clinical decision-making. We accept it could be argued that the exclusion of non-randomised studies provides an incomplete summary of the potential effects of interventions but we maintain the view that a robust systematic review of the evidence for the effectiveness of physiotherapy interventions for CRPS is best established by the inclusion of RCTs only. We remain open to the fact that developments in the science and methodology of systematic reviews might justify the inclusion of data from non-randomised studies, such as from large population databases, in the future (Shea 2017). We included published abstracts and where there were insufficient data for analysis in the abstracts, we attempted to locate the full study (e.g. by contacting the study authors). If the

data from the full study were unavailable, we added the abstract to 'Studies awaiting classification' (see Characteristics of studies awaiting classification table).

Types of participants

We included trials of adults, aged 18 years or older, diagnosed with CRPS I or II, or with an alternative diagnostic label for these conditions (e.g. RSD, causalgia). We grouped trials and analysed data according to diagnosis (i.e. CRPS I and II, or mixed). Since the use of formal diagnostic criteria for CRPS is inconsistent across studies (Reinders 2002), we included trials that used established or validated diagnostic criteria, including the Veldman criteria (Veldman 1993), the International Association for the Study of Pain (IASP) criteria (Merskey 1994), Bruehl criteria (Bruehl 1999), Budapest criteria (Harden 2010), and Atkins criteria (Atkins 2010), as well as studies that either predate these criteria or use non-standard diagnostic criteria.

Types of interventions

We included all randomised controlled comparisons of physiotherapy interventions, employed in either a stand-alone fashion or in combination, compared with placebo, no treatment, another intervention or usual care, or of varying physiotherapy interventions compared with each other, which were aimed at treating pain or disability, or both, associated with CRPS. We included trials in which non-physiotherapists (e.g. occupational therapists) delivered such physiotherapy interventions, as defined in Description of the intervention, and reported the professional discipline of the clinician delivering the intervention. We did not pre-define any specific comparisons in advance as physiotherapy interventions encompass a broad range of potential therapeutic approaches (e.g. various rehabilitation strategies or electrotherapy modalities). After the publication of our Cochrane protocol (Smart 2013), we decided to exclude studies that evaluated non-physiotherapy based interventions (e.g. pharmacological) in which all arms received the same physiotherapy intervention (differing only in the application of the non-physiotherapy component) as they are unlikely to offer any insight into the value of physiotherapy management (see Differences between protocol and review).

Types of outcome measures

Primary outcomes

1. Pain intensity as measured using a visual analogue scale (VAS), numerical rating scale (NRS), verbal rating scale or Likert scale.
2. Disability as measured by validated self-report questionnaires/scales or functional testing protocols.

Secondary outcomes

We planned to analyse the following secondary outcome measures where such data were available:

1. Composite scores for CRPS symptoms.
2. Health-related quality of life (HRQoL) using any validated tool.
3. Patient global impression of change (PGIC) scales.
4. Incidence/nature of adverse effects (AEs).

We excluded studies that did not measure the primary or secondary outcomes of interest described above.

Search methods for identification of studies

Electronic searches

For this update we identified relevant RCTs by electronically searching the following databases:

1. Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, Issue 7 of 12, 2021;
2. MEDLINE (OVID) (1966 to 16 July 2021);
3. EMBASE (OVID) (1974 to 16 July 2021);
4. CINAHL (EBSCO) (1982 to July 2021);
5. PsycINFO (OVID) (1806 to July 2021);
6. LILACS (Bireme) (1982 to July 2021);
7. PEDro (1929 to July 2021);
8. Web of Science (ISI) (1945 to July 2021).

The Information Specialist of the Cochrane Pain, Palliative and Supportive Care Group devised the search strategies and added some extra terms to the strategies for this update. She and the review authors ran these searches. We used a combination of controlled vocabulary, i.e. medical subject headings (MeSH) and free-text terms. The search strategies used for this update and the original review can be found in Appendix 1 and Appendix 2.

Searching other resources

Reference lists

On completion of the electronic searches we searched the reference lists of all eligible studies in order to identify additional relevant studies. In addition we screened the reference lists of previous systematic reviews (Bowering 2013; Daly 2009; O'Connell 2013; Smith 2005).

External experts

We sent the list of included trials to a content expert to help identify any additional relevant studies (November 2020).

Unpublished data

In order to minimise the impact of publication bias we searched the following registers and databases to identify unpublished research as well as research in progress (July to August 2021):

1. OpenGrey (System for Information on Grey Literature in Europe);
2. ProQuest Dissertations & Theses Global (formerly Dissertation Abstracts (ProQuest));
3. National Research Register Archive;
4. Health Services Research Projects in Progress;
5. Current Controlled Trials Register (incorporating the meta-register of controlled trials and the International Standard Randomised Controlled Trial Number);
6. ClinicalTrials.gov;
7. International Clinical Trials Registry Platform;
8. Pan African Clinical Trials Registry;
9. EU Clinical Trials Register.

Data collection and analysis

Selection of studies

Two review authors (KMS and BMW in the original review and KMS and MCF in this updated review) independently assessed the titles and abstracts of studies we identified by the search strategy for eligibility. If the eligibility of a trial was unclear from the title and abstract, we assessed the full-text article. We obtained potentially relevant studies identified in the first round of screening in full text and independently assessed these for inclusion using the same process outlined above. We excluded trials that did not match the inclusion criteria (see the Criteria for considering studies for this review section). We resolved any disagreements between review authors regarding a study's inclusion by discussion. If we could not resolve disagreements, a third review author (NOC) assessed relevant studies and we made a majority decision. Trials were not anonymised prior to assessment. We did not apply any language restrictions.

Data extraction and management

Two review authors (KMS and BMW in the original review and KMS and MCF in this updated review) independently extracted data from all included trials. We extracted data using a standardised and piloted form. We resolved any discrepancies and disagreements by consensus. In cases where we could not achieve consensus, a third review author (NOC) assessed the trial and we took a majority decision. We extracted the following data from each included trial:

1. country of origin;
2. study design;
3. study population (including diagnosis, diagnostic criteria used, symptom duration, age range, gender split);
4. type of noxious initiating event: surgery, fracture, crush injury, projectile, stab injury, other or no event;
5. type of tissue injured: nerve, soft tissue, bone;
6. presence of medico-legal factors (that may influence the experience of pain and the outcomes of therapeutic interventions);
7. concomitant treatments that may affect outcome: medication, procedures etc.;
8. sample size: active and control/comparator groups;
9. intervention (including type, parameters (e.g. frequency, dose, duration), setting and professional discipline of the clinician delivering the therapy);
10. type of placebo/comparator intervention;
11. outcomes (primary and secondary) and time points assessed;
12. adverse effects;
13. author conflict of interest statements and study funding source;
14. assessment of risk of bias.

Assessment of risk of bias in included studies

We assessed the overall risk of bias for each included trial on the basis of an evaluation of key domains using a modified version of the Cochrane risk of bias assessment tool. We classified risk of bias as either 'low' (low risk of bias for all key domains), 'unclear' (unclear risk of bias for one or more key domains) or 'high' (high risk of bias for one or more key domains) (items 1 to 8 and 11 below), as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). We also considered experimental design-specific (e.g. cross-over study designs) risk of bias issues where appropriate (Higgins 2011b). We also evaluated included trials for the additional sources of bias associated with sample size and duration of follow-up, as recommended by Moore 2010 (items 9 and 10 below). Small studies are more prone to bias because of their inherent imprecision and due to the effects of publication biases (Dechartres 2013; Moore 2012; Nüesch 2010). Inadequate length of follow-up may produce an overly positive view of the true clinical effectiveness of interventions, particularly in persistent conditions (Moore 2010). These additional criteria were not considered 'key domains' and therefore did not inform judgements of a trial's overall risk of bias. We assessed the following key and non-key domains of risks of bias for each included trial using either 'low', 'unclear' or 'high' judgements according to the following criteria:

1. Random sequence generation (checking for possible selection bias). We assessed the method used to generate the allocation sequence as either: low risk of bias (any truly random process, e.g. random number table; computer random number generator); unclear risk of bias (method used to generate sequence not clearly stated); or high risk of bias (studies on closer inspection using a quasi/non-random process, e.g. odd or even date of birth; hospital or clinic record number).
2. Allocation concealment (checking for possible selection bias). The method used to conceal allocation to group prior to assignment determines whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment. We assessed the methods used as: low risk of bias (e.g. telephone or central randomisation; consecutively numbered, sealed, opaque envelopes); unclear risk of bias (method not clearly stated); or high risk of bias (studies that do not adequately conceal allocation, e.g. open list).
3. Blinding of study participants and personnel (checking for possible performance bias). We assessed the methods used to blind participants and care providers as either: low risk of bias (participants and care providers blinded to allocated intervention and unlikely that blinding broken; or no/incomplete blinding but judged that both intervention arms reflect active interventions of relatively equal credibility delivered with equal enthusiasm); unclear risk of bias (insufficient information provided to permit a judgement of low/high risk of bias); or high risk of bias (participants and care providers not blinded to the allocated intervention and interventions are clearly identifiable as control and experimental; or participants and care providers blinded to the allocated intervention but likely that blinding was broken).
4. Blinding of outcome assessment (self-reported outcomes) (checking for possible detection bias). We assessed the methods used to blind study participants self-reporting outcomes (e.g. pain severity) from knowledge of which intervention a participant received. We assessed the methods as either: low risk of bias (participants blinded to allocated intervention and unlikely that blinding broken; or no/incomplete blinding but judged that both intervention arms reflect active interventions of relatively equal credibility delivered with equal enthusiasm); unclear risk of bias (insufficient information provided to permit a judgement of low/high risk of bias); or high risk of bias (participants not blinded to the allocated intervention and interventions are clearly identifiable as control

and experimental; or participants blinded to the allocated intervention but likely that blinding was broken).

5. Blinding of outcome assessment (investigator-administered outcomes) (checking for possible detection bias). We assessed the methods used to blind researchers undertaking outcome assessments (e.g. functional testing protocols) from knowledge of which intervention a participant received. We assessed the methods as at either: low risk of bias (researchers blinded to allocated intervention and unlikely that blinding broken); unclear risk of bias (insufficient information provided to permit a judgement of low/high risk of bias); high risk of bias (researchers not blinded to the allocated intervention; or researcher blinded to the allocated intervention but likely that blinding was broken).
6. Incomplete outcome data (dropout) (checking for possible attrition bias). We first assessed for risk of attrition bias by evaluating participant dropout rates according to judgements based on the following criteria: low risk of bias (less than 20% dropout and appears not to be systematic, with numbers for each group and reasons for dropout reported); unclear risk of bias (less than 20% dropout but appears to be systematic or numbers per group and reasons for dropout not reported); high risk of bias (greater than or equal to 20% dropout).
7. Incomplete outcome data (method of analysis) (participants analysed in the group to which they were allocated) (checking for possible attrition bias). We further assessed for risk of attrition bias by separately evaluating the appropriateness of the method of analysis employed, using the following criteria: low risk of bias (participants analysed in the group to which they were allocated (intention-to-treat (ITT) or as an available case analysis); unclear risk of bias (insufficient information provided to determine if analysis was based on the principle of ITT or per protocol); or high risk of bias (if per protocol analysis used or where available data is not analysed or participant data were included in a group to which they were not originally assigned to).
8. Selective reporting (checking for possible reporting bias). We assessed studies for selective outcome reporting using the following judgements: low risk of bias (study protocol available and all pre-specified primary outcomes of interest adequately reported or study protocol not available but all expected primary outcomes of interest adequately reported or all primary outcomes numerically reported with point estimates and measures of variance for all time points); unclear risk of bias (insufficient information provided to permit a judgement of low/high risk of bias); or high risk of bias (incomplete reporting of pre-specified primary outcomes or point estimates and measures of variance for one or more primary outcome not reported numerically (e.g. graphically only) or one or more primary outcomes reported using measurements, analysis methods or subsets of data that were not pre-specified or one or more reported primary outcomes were not pre-specified or results for a primary outcome expected to have been reported were excluded).
9. Sample size (checking for possible biases confounded by small sample size): we assessed trials as being at low risk of bias (greater than or equal to 200 participants per treatment arm); unclear risk of bias (50 to 199 participants per treatment arm); high risk of bias (less than 50 participants per treatment arm).
10. Duration of follow-up (checking for possible biases confounded by a short duration of follow-up): we assessed trials as being at low risk of bias (follow-up of greater than or equal to eight weeks); unclear risk of bias (follow-up of two to seven weeks); or high risk of bias (follow-up of less than two weeks).
11. Other bias. We assessed studies for other potential sources of bias. We determined judgements regarding low/unclear/high risk of bias according to the potential confounding influence of identified factors, for example: low risk of bias (appears free of other potentially serious sources of bias e.g. no serious study protocol violations identified); unclear risk of bias (other sources of bias may be present but there is either insufficient information to assess whether an important risk of bias exists or insufficient rationale or evidence regarding whether an identified problem will introduce bias); or high risk of bias (results may have been confounded by at least one potentially serious risk of bias, e.g. a significant baseline imbalance between groups; a serious protocol violation; use of 'last observation carried forward' when dealing with missing data).

Two review authors (KMS and BMW in the original review and KMS and MCF in this updated review) independently undertook the risk of bias assessments, and resolved any disagreements by discussion. If they could not reach an agreement, a third review author (NOC) undertook a risk of bias assessment and we took a majority decision.

Measures of treatment effect

We expressed the size of treatment effect on pain intensity, as measured with a VAS or NRS, using the mean difference (MD) (where all studies utilised the same measurement scale) or the standardised mean difference (SMD) (where studies used different scales) based on the approach described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2011). Effect sizes were also expressed as a proportion of average baseline values. In order to aid interpretation of the pooled effect size we planned to back-transform the SMD value to a 0 to 100 mm VAS format on the basis of the mean standard deviation (SD) from trials using a 0 to 100 mm VAS where possible.

We presented and analysed primary outcomes as change on a continuous scale or in a dichotomised format as the proportion of participants in each group who attained a predetermined threshold of improvement. For example, we judged cut-points from which to interpret the likely clinical importance of (pooled) effect sizes according to provisional criteria proposed in the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) consensus statement (Dworkin 2008). Specifically, we judged reductions in pain intensity compared with baseline as follows:

1. less than 15%: 'no important change';
2. 15% or more: 'minimally important change';
3. 30% or more: 'moderately important change';
4. 50% or more: 'substantially important change'.

We planned to use the cut-points for 'minimally', 'moderately' and 'substantially' important changes to generate dichotomous outcomes, the effect size for which we would have expressed as the risk ratio (or relative risk (RR)) but a lack of data did not permit any such analyses.

The IMMPACT thresholds are based on estimates of the degree of within-person change from baseline that participants might consider clinically important. In a change to our original protocol (Smart 2013) and systematic review (Smart 2016), we extended our interpretation of changes in outcomes to include between-group differences (see Differences between protocol and review). There is little consensus or evidence regarding cut-points from which to interpret the magnitude of clinically important differences in pain intensity (or other patient-related outcome measures) based on the between-group difference post-intervention (Dworkin 2009). For the purpose of this systematic review we adopted the recommendations of the OMERACT 12 group, with a threshold of 10 mm on a 0 mm to 100 mm VAS as being the threshold for minimal importance for average between-group change (Busse 2015). Busse 2015 also suggests some more nuanced interpretations of between-group changes, with pooled estimates of i) ≥ 2.0 units suggesting a large treatment effect, ii) 1.0 to 1.9 suggesting an important effect, iii) 0.5 to 1.0 suggesting the treatment may benefit an appreciable number of patients, and iv) ≤ 0.5 suggesting a small to very small effect. We interpreted our estimates of treatment effect according to these thresholds but did so appropriately and cautiously.

We planned to present secondary outcomes as change on a continuous scale or in a dichotomised format but a lack of data did not permit any such analyses.

We analysed the data using Review Manager (RevMan) (RevMan 2014). We plotted the results of each RCT with available data as point estimates with corresponding 95% CIs and displayed them using forest plots. If included trials demonstrated clinical homogeneity we performed a meta-analysis to quantify the pooled treatment effect sizes using a random-effects model. We did not perform a meta-analysis when clinical heterogeneity was present. Similarly we presented secondary outcomes, though we did not consider them for meta-analysis.

Unit of analysis issues

All included trials randomised participants at the individual participant level. We planned to meta-analyse estimates of treatment effect (and their standard errors (SE)) from cluster-RCTs employing appropriate statistical analyses using the generic inverse-variance method in RevMan (RevMan 2014), as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). Where we considered such trials to have employed inappropriate analyses, we planned to utilise methods for 'approximately correct analysis' where possible (Higgins 2011b). In addition, we planned to enter cross-over trials into a meta-analysis when it was clear that data were free from carry-over effects, and to combine the results of cross-over trials with those of parallel trials by imputing the post-treatment between-condition correlation coefficient from an included trial that presented individual participant data and use this to calculate the SE of the SMD. These data may be entered into a meta-analysis using the generic inverse-variance method (Higgins 2011b).

Dealing with missing data

We attempted to contact the authors of included trials when numerical data were unreported or incomplete. If trial authors only presented data in graphical form, we did not attempt to extract the data from the figures. If SD values were missing from follow-up assessments but were available at baseline, we used these values as estimates of variance in the follow-up analyses.

Assessment of heterogeneity

We evaluated the included trials for clinical homogeneity regarding study population, treatment procedure, control intervention, timing of follow-up and outcome measurement. For trials that were sufficiently clinically homogenous to pool, we formally explored heterogeneity using the Chi^2 test to investigate the statistical significance of any heterogeneity, and the I^2 statistic to estimate the amount of heterogeneity. We interpreted I^2 values according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011):

- 0% to 40%: heterogeneity might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

Assessment of reporting biases

We planned to test for the possible influence of publication bias on trials that utilised dichotomised outcomes by estimating the number of participants in trials with zero effect required to change the number needed to treat (NNT) to an unacceptably high level (defined as an NNT of 10), as outlined by Moore 2008. An absence of relevant data meant that we did not undertake any analyses. Instead, we considered the possible influence of small study/publication biases on review findings as part of our risk of bias assessment (see the Assessment of risk of bias in included studies section) and as part of our Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessments of the certainty of evidence (see the Data synthesis section) (Guyatt 2011a). We may include such analyses in future updates of this Cochrane Review where relevant data are available.

Data synthesis

Where possible, we grouped extracted data according to diagnosis (CRPS types I or II, or mixed), intervention, outcome (i.e. pain, disability) and duration of follow-up (short-term: zero to less than two weeks post intervention; mid-term: two to seven weeks post intervention; and long-term: eight or more weeks post intervention). Regarding intervention, we planned to pool data from trials that investigated the same single therapy separately for each therapy. We planned to pool trials of multimodal physiotherapy programmes together.

For all analyses, we report the outcome of the risk of bias assessments. Where we found inadequate data to support statistical pooling, we performed a narrative synthesis of the evidence.

Subgroup analysis and investigation of heterogeneity

Where significant heterogeneity (P value < 0.1) was present, we planned to explore subgroup analyses (see the Differences between protocol and review section). We planned to perform subgroup analyses based on the type of CRPS (i.e. I, II or mixed) and its temporal characteristics (i.e. acute (defined as symptoms and signs of CRPS of zero to 12 weeks duration) and chronic (symptoms and signs of CRPS lasting 13 weeks)). However, we did not undertake them due to the insufficient number of included trials.

Sensitivity analysis

We planned to conduct a sensitivity analysis based on risk of bias (investigating the influence of excluding studies classified at high risk of bias).

Summary of findings and assessment of the certainty of the evidence

We conducted a qualitative analysis of all trial findings and used the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach to assess and rank the certainty of evidence (Guyatt 2011a; Guyatt 2011b).

To ensure consistency of GRADE judgements we applied the following assessment criteria:

1. Serious study limitations: we downgraded once if more than 25% of the participants were from trials we classified as being at overall high risk of bias, as described in the Assessment of risk of bias in included studies section.
2. Inconsistency: we downgraded once if heterogeneity was statistically significant and the I^2 statistic value was greater than 40%. When a meta-analysis was not performed we downgraded once if the trials did not show effects in the same direction.
3. Indirectness: we downgraded once if more than 50% of the participants were outside the target group.
4. Imprecision: we downgraded once if there were fewer than 400 participants for continuous data and fewer than 300 events for dichotomous data.
5. Publication bias: we downgraded once where there was direct evidence of publication bias or if estimates of effect based on small-scale, industry-sponsored studies raised a high index of suspicion of publication bias.

Two review authors (KMS and MCF) made the judgement of whether these factors were present or not. We considered single trials to be inconsistent and imprecise, unless more than 400 participants were randomised for continuous outcomes or more than 300 for dichotomous outcomes. We applied the following definitions regarding the certainty of the evidence (Balshem 2011):

1. High: we are very confident that the true effect lies close to that of the estimate of the effect.
2. Moderate: we are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
3. Low: our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
4. Very low: we have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

Summary of findings table

At the time of protocol development we did not specify any key comparisons of interventions (Smart 2013). In light of the wide range of trial interventions identified and the very limited data available we have taken the post hoc decision to present summary of findings tables for our primary outcomes of pain and disability, together with adverse effects, for the comparisons 'Physiotherapy compared to minimal care for adults with CRPS I and CRPS II' and included trials that delivered what we determined to be conventional multimodal physiotherapy, reflective of common clinical practice (Miller 2019).

We have not presented summary of findings tables for all identified comparisons of interventions as these are, we judge, too numerous, most often involving single trials with small samples and minimal to no data presented, and therefore of limited clinical use. However, we have considered the findings from all included trials with respect to all our outcomes of interest in full in the Effects of interventions section.

RESULTS

Description of studies

See the Characteristics of included studies and Characteristics of excluded studies.

Results of the search

Our updated search period extended from February 2015, the time point up to which our original search was conducted, to July 2021. We identified 634 records from the database searches and one additional record from an author whom we contacted with a query. After de-duplication (n = 149) we screened 486 abstracts from which we assessed 38 full-text articles for eligibility. A total of 16 studies met our inclusion criteria (see Characteristics of included studies table). We have presented a flow diagram outlining the trial screening and selection process (Figure 1).

Figure 1. Study flow diagram.

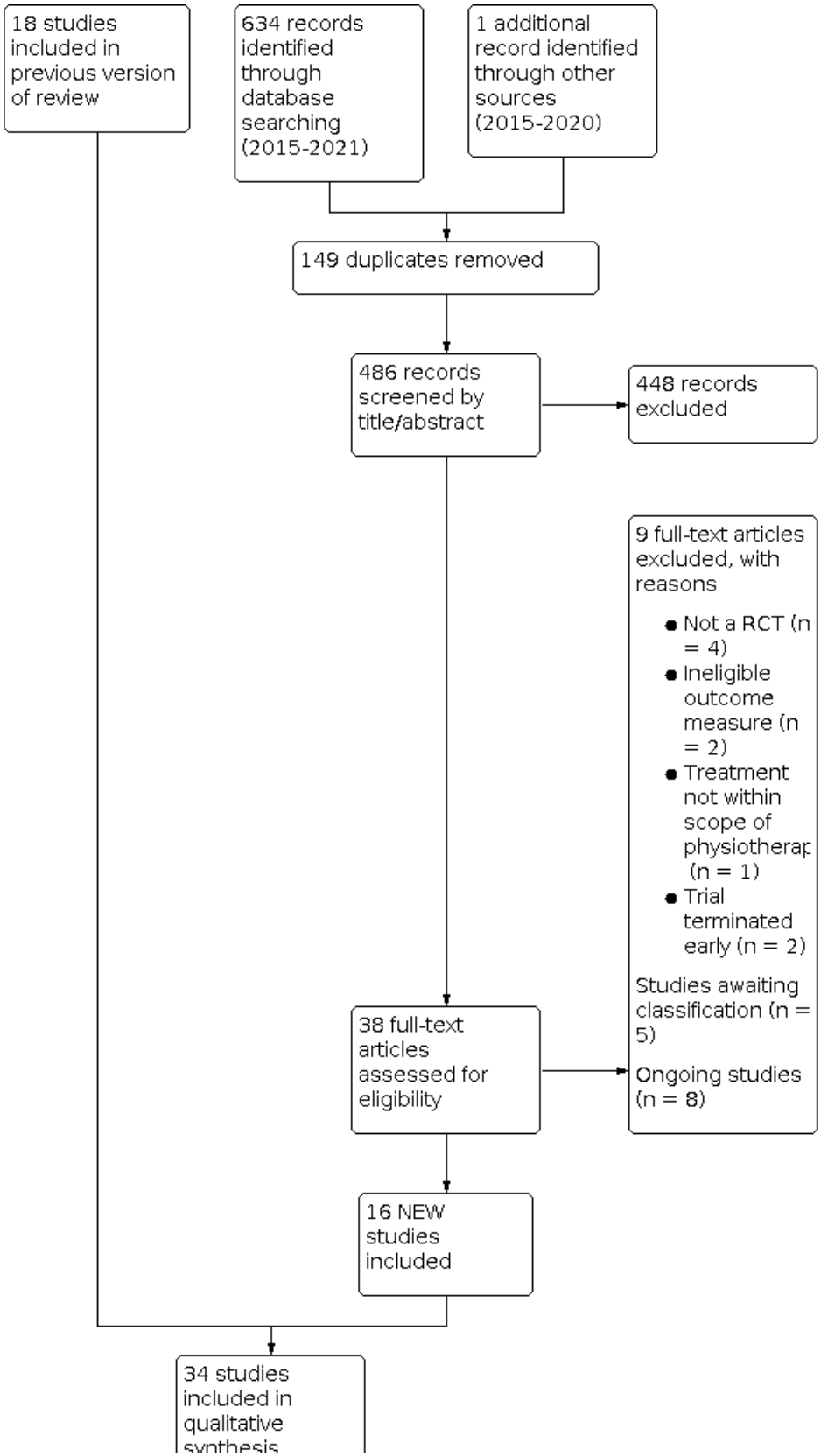
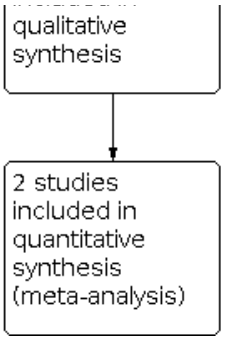


Figure 1. (Continued)



We combined the 16 trials (600 participants) identified in our updated literature search with the 18 trials (739 participants) included within our original review (Smart 2016). From the combined total of 1230 records screened and 80 full-text reviews across the two searches, we included 34 trials involving 1339 participants in this review.

Included studies

We included 34 trials in this review, 18 from the original review (Smart 2016) (Askin 2014; Aydemir 2006; Cacchio 2009a; Cacchio 2009b; Dimitrijevic 2014; Duman 2009; Durmus 2004; Hazneci 2005; Jeon 2014; Li 2012; Moseley 2004; Moseley 2005; Moseley 2006; Moseley 2009; Mucha 1992; Oerlemans 1999; Schreuders 2014; Uher 2000), and 16 from the updated searches (Barnhoorn 2015; Benedetti 2018; Bilgili 2016; Büyükturan 2018; den Hollander 2016; Devrimsel 2015; Halicka 2021; Hwang 2014; Lewis 2021; Ozcan 2019; Ryan 2017; Saha 2021; Sarkar 2017; Strauss 2021; Topcuoglu 2015; Vural 2016). We have provided the details of all included trials in the Characteristics of included studies table.

In our original review we contacted 10 authors for missing data (Cacchio 2009b; Jeon 2014; Moseley 2004; Moseley 2005; Moseley 2006; Moseley 2009; Mucha 1992; Oerlemans 1999; Schreuders 2014; Uher 2000). One trial author responded and supplied data for an outcome measure of 'impairment' but we were unable to extract outcome data linked to 'pain intensity' from the supplied data (Oerlemans 1999). One trial author responded, stating that they were unable to supply the relevant data (Schreuders 2014). There was no response from the other trial authors we had contacted. In this updated review, we contacted 10 authors for missing data (den Hollander 2016; Halicka 2021; Hwang 2014; Lewis 2021; Ozcan 2019; Ryan 2017; Sarkar 2017; Strauss 2021; Topcuoglu 2015; Vural 2016). Five authors supplied missing data (den Hollander 2016; Halicka 2021; Ryan 2017; Sarkar 2017; Strauss 2021). One author replied to report that they did not have the data (Vural 2016). One author replied indicating that they would look into our request but did not subsequently supply the data (Ozcan 2019). There was no response from the remaining three authors (Hwang 2014; Lewis 2021; Topcuoglu 2015).

Design

All included trials were RCTs, and 32 essentially used a parallel-group design. Whilst the selected participants in three trials crossed over from comparator to intervention groups (Cacchio 2009b; Moseley 2004; Mucha 1992), none employed a true randomised cross-over design and we analysed them up to the point of cross-over as parallel-group designs. Two trials employed a within-subject randomised cross-over design (Moseley 2009; Strauss 2021). The majority of included trials (26 out of 34) included two intervention arms, seven trials included three arms (Askin 2014; Aydemir 2006; Cacchio 2009b; Hwang 2014; Moseley 2005; Oerlemans 1999; Sarkar 2017), and one study used four arms (Moseley 2009). No cluster-RCTs met the inclusion criteria of this Cochrane Review.

Setting

Trials were undertaken across a range of geographical locations including: Turkey (n = 11); Australia and the Netherlands (n = 4 each); Germany, Italy and the United Kingdom (n = 3 each), India and South Korea (n = 2 each); China, India and Serbia (n = 1 each). Three (9%) were multi-centre trials (Halicka 2021; Lewis 2021; Oerlemans 1999), nine (28%) trials did not report whether they were single- or multi-centre (Cacchio 2009b; Devrimsel 2015; Duman 2009; Moseley 2005; Moseley 2006; Moseley 2009; Mucha 1992; Schreuders 2014; Uher 2000), and the remaining 22 (65%) were all single-centre trials.

Participants

The 34 trials included a total of 1339 participants and the total number of participants per trial ranged from eight (Ryan 2017) to 135 (Oerlemans 1999). Thirty trials included participants with CRPS I using a range of diagnostic criteria, most commonly using those of Bruehl 1999 and Harden 2007; Harden 2010. One trial included participants with CRPS II (Strauss 2021) and one trial included participants with CRPS type I and II but did not report the numbers with each type (Hwang 2014). Two trials did not specify the type of CRPS for their participants (Lewis 2021; Sarkar 2017).

Twenty-four trials included participants with CRPS I of the upper limb (Askin 2014; Aydemir 2006; Bilgili 2016; Büyükturan 2018; Cacchio 2009a; Cacchio 2009b; Devrimsel 2015; Duman 2009; Durmus 2004; Halicka 2021; Hazneci 2005; Lewis 2021; Li 2012; Moseley 2004; Moseley 2005; Moseley 2009; Mucha 1992; Oerlemans 1999; Ozcan 2019; Ryan 2017; Saha 2021; Schreuders 2014; Topcuoglu 2015; Vural 2016), seven with either upper or lower limb CRPS I (Barnhoorn 2015; Benedetti 2018; den Hollander 2016; Dimitrijevic 2014; Hwang 2014; Moseley 2006; Sarkar 2017), one with CRPS I of the lower limb (Uher 2000) and one trial included participants with either upper, lower, multi-limb or whole body CRPS I (Jeon 2014). In the trials where the type of CRPS was not specified, one study included participants with upper limb CRPS (Lewis 2021) and one included participants with upper and lower limb CRPS (Sarkar 2017). Participants developed CRPS I linked to a range of aetiologies including onset post fracture, soft-tissue

injuries, stroke, surgery, carpal tunnel syndrome as well as of idiopathic onset.

Participants had acute symptoms (less than or equal to three months) of CRPS I in eight trials (Büyükturan 2018; Cacchio 2009a; Devrimsel 2015; Dimitrijevic 2014; Durmus 2004; Hazneci 2005; Li 2012; Mucha 1992), chronic symptoms (greater than three months) in 14 trials (Barnhoorn 2015; den Hollander 2016; Duman 2009; Halicka 2021; Hwang 2014; Jeon 2014; Lewis 2021; Moseley 2004; Moseley 2005; Moseley 2006; Moseley 2009; Ryan 2017; Saha 2021; Schreuders 2014), and a mix of acute and chronic symptoms in six trials (Askin 2014; Benedetti 2018; Oerlemans 1999; Sarkar 2017; Topcuoglu 2015; Vural 2016). Five trials involving participants with CRPS I did not report the duration of symptoms (Aydemir 2006; Bilgili 2016; Cacchio 2009b; Ozcan 2019; Uher 2000). Participants had chronic symptoms in the one trial involving those with CRPS II (Strauss 2021).

Interventions and comparators

We have provided a detailed description of the interventions delivered in each included trial in the Characteristics of included studies table. The types of physiotherapy interventions delivered were heterogeneous across the included trials and included various electro-physical modalities (ultrasound, TENS, laser, interferential therapy, pulsed electromagnetic field therapy, whirlpool baths, neuromuscular electrical stimulation, fluidotherapy, contrast baths), cortically-directed sensory-motor rehabilitation strategies (GMI, mirror therapy, virtual body swapping, tactile sensory discrimination training, prism adaptation treatment), exercise (active, active-assisted, passive, stretching, strengthening, mobilising, functional; supervised and unsupervised), cognitive-behavioural interventions ('exposure-based' strategies), manual lymphatic drainage (MLD) and pain management advice. Twelve trials evaluated electro-physical modalities (Askin 2014; Aydemir 2006; Benedetti 2018; Bilgili 2016; Büyükturan 2018; Devrimsel 2015; Dimitrijevic 2014; Durmus 2004; Hazneci 2005; Mucha 1992; Ozcan 2019; Ryan 2017), 15 trials evaluated cortically-directed sensory-motor rehabilitation strategies (Cacchio 2009a; Cacchio 2009b; Halicka 2021; Hwang 2014; Jeon 2014; Lewis 2021; Moseley 2004; Moseley 2005; Moseley 2006; Moseley 2009; Saha 2021; Sarkar 2017; Schreuders 2014; Strauss 2021; Vural 2016), three trials evaluated aerobic exercise or general rehabilitation therapies (Li 2012; Oerlemans 1999; Topcuoglu 2015), two trials evaluated MLD (Duman 2009; Uher 2000) and two trials evaluated cognitive-behavioural/exposure-based interventions (Barnhoorn 2015; den Hollander 2016). Eleven trials directly compared an active and placebo intervention (Askin 2014; Aydemir 2006; Benedetti 2018; Bilgili 2016; Büyükturan 2018; Cacchio 2009a; Cacchio 2009b; Durmus 2004; Halicka 2021; Lewis 2021; Ryan 2017), and 22 trials compared the experimental intervention to an active comparator. Of these, 11 trials compared the experimental intervention to 'conventional treatment' (Barnhoorn 2015; den Hollander 2016; Duman 2009; Li 2012; Moseley 2004; Moseley 2006; Ozcan 2019; Saha 2021; Schreuders 2014; Topcuoglu 2015; Vural 2016), and 11 trials compared the experimental intervention to various other active comparators (Devrimsel 2015; Dimitrijevic 2014; Hazneci 2005; Hwang 2014; Jeon 2014; Moseley 2005; Moseley 2009; Mucha 1992; Oerlemans 1999; Sarkar 2017; Uher 2000). One cross-over trial compared the experimental intervention to a waiting list control (Strauss 2021).

Excluded studies

We excluded nine full-text trial reports from the updated searches, in addition to the 13 excluded from the original review, because they were not RCTs (n = 4), investigated outcome measures that were not of interest (n = 2), were terminated early (n = 2) or tested interventions that fell outside the scope of physiotherapy (n = 1) (see Characteristics of excluded studies).

Studies awaiting classification

Eight trials are awaiting classification (see Characteristics of studies awaiting classification). At the time the searches for the current review update were undertaken (July 2021) four trials had only been published as conference abstracts (Dimitrijevic 2019; Dimitrijevic 2020; Mallikarjunaiah 2015; Patru 2017). We were unable to make contact with the authors of three trials to ascertain their status (ISRCTN39729827; ISRCTN97144266; NCT01944150) and one trial had been delayed (UKCRN ID 12602).

Ongoing studies

We identified seven potentially relevant ongoing studies that are either completed and being analysed (NCT03377504; NCT03887962), ongoing (NCT02395211; NCT02753335), delayed (JPRN-UMIN000029801), or whose progress is unknown (ChiCTR1900020835; CTRI/2019/01/017272) (see Characteristics of ongoing studies).

Risk of bias in included studies

We have summarised risk of bias results for all included trials in Figure 2 and Figure 3. We judged the overall risk of bias, based on evaluations of key domains (i.e. random sequence generation, allocation concealment, blinding of study participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias) as being 'high' for 27 trials (Askin 2014; Barnhoorn 2015; Bilgili 2016; Büyükturan 2018; Cacchio 2009b; den Hollander 2016; Dimitrijevic 2014; Duman 2009; Halicka 2021; Jeon 2014; Lewis 2021; Li 2012; Moseley 2004; Moseley 2005; Moseley 2006; Moseley 2009; Mucha 1992; Oerlemans 1999; Ozcan 2019; Ryan 2017; Saha 2021; Sarkar 2017; Schreuders 2014; Strauss 2021; Topcuoglu 2015; Uher 2000; Vural 2016), and 'unclear' for seven trials (Aydemir 2006; Benedetti 2018; Cacchio 2009a; Devrimsel 2015; Durmus 2004; Hazneci 2005; Hwang 2014). We did not judge any of the included trials as having an overall 'low' risk of bias.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included trials.

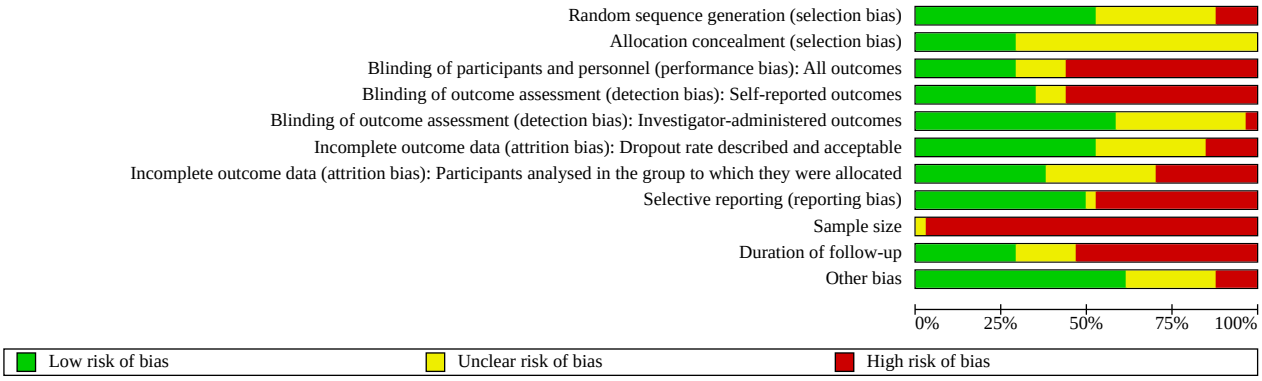


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included trial.

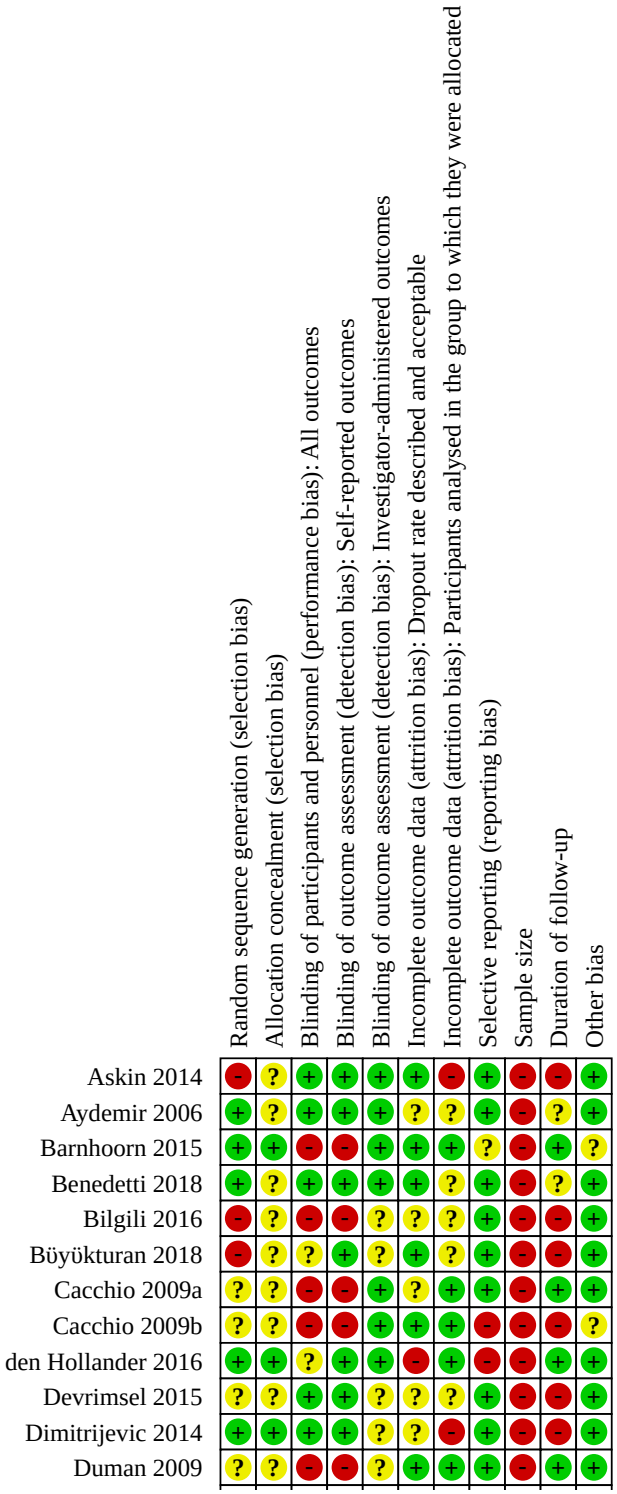
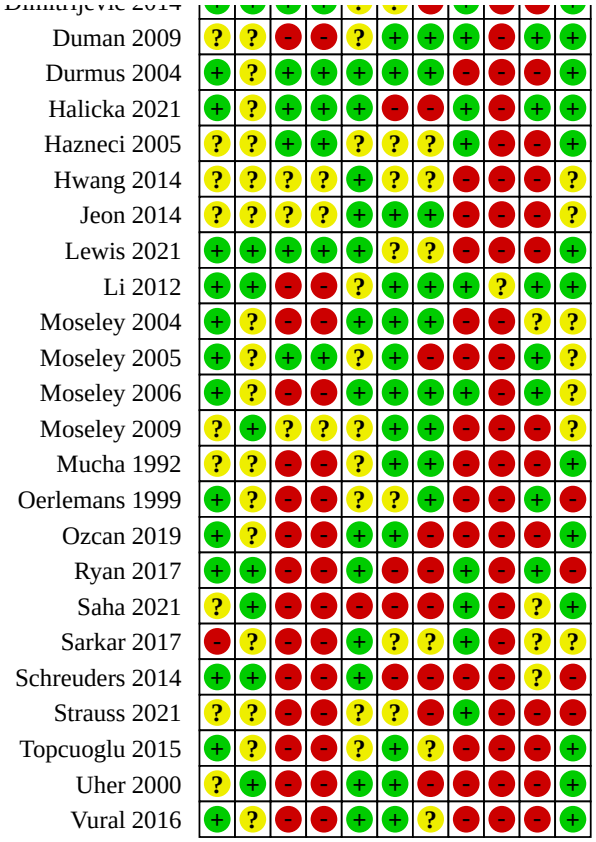


Figure 3. (Continued)



Allocation

Random sequence generation

We judged 18 trials to be at low risk of bias as the methods used to generate the random sequence were adequately described (Aydemir 2006; Barnhoorn 2015; Benedetti 2018; den Hollander 2016; Dimitrijevic 2014; Durmus 2004; Halicka 2021; Lewis 2021; Li 2012; Moseley 2004; Moseley 2005; Moseley 2006; Oerlemans 1999; Ozcan 2019; Ryan 2017; Schreuders 2014; Topcuoglu 2015; Vural 2016), and 12 to be at unclear risk of bias because insufficient information was provided on the process for random sequence generation (Cacchio 2009a; Cacchio 2009b; Devrimsel 2015; Duman 2009; Hazneci 2005; Hwang 2014; Jeon 2014; Moseley 2009; Mucha 1992; Saha 2021; Strauss 2021; Uher 2000). Four trials used a quasi-randomisation method and we judged these to be at high risk of bias (Askin 2014; Bilgili 2016; Büyükturan 2018; Sarkar 2017).

Allocation concealment

We judged 10 trials to be at low risk of bias because the methods for concealing allocation were adequately described (Barnhoorn 2015; den Hollander 2016; Dimitrijevic 2014; Lewis 2021; Li 2012; Moseley 2009; Ryan 2017; Saha 2021; Schreuders 2014; Uher 2000), and 24 to be at unclear risk of bias because insufficient information was provided about how allocation was concealed (Askin 2014; Aydemir 2006; Benedetti 2018; Bilgili 2016; Büyükturan 2018; Cacchio 2009a; Cacchio 2009b; Devrimsel 2015; Duman 2009; Durmus 2004; Halicka 2021; Hazneci 2005; Hwang 2014; Jeon 2014; Moseley 2004; Moseley 2005; Moseley 2006; Mucha 1992; Oerlemans 1999; Ozcan 2019; Sarkar 2017; Strauss 2021; Topcuoglu 2015; Vural 2016).

Blinding

Blinding of study participants and personnel

We judged 10 trials to be at low risk of bias where participants and personnel were adequately blinded to the intervention or where we considered a lack of blinding to have been unlikely to have biased trial outcomes (Askin 2014; Aydemir 2006; Benedetti 2018; Devrimsel 2015; Dimitrijevic 2014; Durmus 2004; Halicka 2021; Hazneci 2005; Lewis 2021; Moseley 2005), and five to be at unclear risk of bias where there was insufficient information provided to permit a judgement of low/high risk of bias (Büyükturan 2018; den Hollander 2016; Hwang 2014; Jeon 2014; Moseley 2009). We judged 19 trials to have a high risk of bias because of inadequate or a lack of blinding (Barnhoorn 2015; Bilgili 2016; Cacchio 2009a; Cacchio 2009b; Duman 2009; Li 2012; Moseley 2004; Moseley 2006; Mucha 1992; Oerlemans 1999; Ozcan 2019; Ryan 2017; Saha 2021; Sarkar 2017; Schreuders 2014; Strauss 2021; Topcuoglu 2015; Uher 2000; Vural 2016).

Blinding of outcome assessment (self-reported outcomes)

We judged 12 trials to be at low risk of bias because they successfully blinded participants who self-reported outcomes (Askin 2014; Aydemir 2006; Benedetti 2018; Büyükturan 2018; den Hollander 2016; Devrimsel 2015; Dimitrijevic 2014; Durmus 2004; Halicka 2021; Hazneci 2005; Lewis 2021; Moseley 2005), and three to

be at unclear risk of bias where there was insufficient information provided to permit a judgement of low/high risk of bias (Hwang 2014; Jeon 2014; Moseley 2009). We judged 19 trials to have a high risk of bias because of inadequate or a lack of blinding of participants who self-reported outcomes (Barnhoorn 2015; Bilgili 2016; Cacchio 2009a; Cacchio 2009b; Duman 2009; Li 2012; Moseley 2004; Moseley 2006; Mucha 1992; Oerlemans 1999; Ozcan 2019; Ryan 2017; Saha 2021; Sarkar 2017; Schreuders 2014; Strauss 2021; Topcuoglu 2015; Uher 2000; Vural 2016).

Blinding of outcome assessment (investigator-administered outcomes)

We judged 20 trials to be at low risk of bias either because they successfully blinded outcome assessors or where the trialists did not employ any investigator-administered outcomes (Askin 2014; Aydemir 2006; Barnhoorn 2015; Benedetti 2018; Cacchio 2009a; Cacchio 2009b; den Hollander 2016; Durmus 2004; Halicka 2021; Hwang 2014; Jeon 2014; Lewis 2021; Moseley 2004; Moseley 2006; Ozcan 2019; Ryan 2017; Sarkar 2017; Schreuders 2014; Uher 2000; Vural 2016). We judged 13 trials to be at unclear risk of bias where there was insufficient information provided to permit a judgement of low/high risk of bias (Bilgili 2016; Büyükturan 2018; Devrimsel 2015; Dimitrijevic 2014; Duman 2009; Hazneci 2005; Li 2012; Moseley 2005; Moseley 2009; Mucha 1992; Oerlemans 1999; Strauss 2021; Topcuoglu 2015). We judged one trial to have a high risk of bias because of a lack of blinding of investigator-administered outcomes (Saha 2021).

Incomplete outcome data (dropout)

Eighteen trials either had no dropouts or a dropout rate of less than 20% and as such we judged them as having a low risk of attrition bias secondary to dropouts (Askin 2014; Barnhoorn 2015; Benedetti 2018; Büyükturan 2018; Cacchio 2009b; Duman 2009; Durmus 2004; Jeon 2014; Li 2012; Moseley 2004; Moseley 2005; Moseley 2006; Moseley 2009; Mucha 1992; Ozcan 2019; Topcuoglu 2015; Uher 2000; Vural 2016). In 11 trials the risk of attrition bias was unclear either because the dropout rate was not reported (Aydemir 2006; Bilgili 2016; Devrimsel 2015; Hazneci 2005; Hwang 2014; Sarkar 2017), or the dropout rate between groups was unequal or the reasons for dropouts were only partially explained and we were unsure of the impact on the trial's results (Cacchio 2009a; Dimitrijevic 2014; Lewis 2021; Oerlemans 1999; Strauss 2021). Five trials with overall dropout rates of ≥ 20% had a high risk of attrition bias (den Hollander 2016; Halicka 2021; Ryan 2017; Saha 2021; Schreuders 2014).

Incomplete outcome data (participants analysed in the group to which they were allocated)

We judged 13 trials (Barnhoorn 2015; Cacchio 2009a; Cacchio 2009b; den Hollander 2016; Duman 2009; Durmus 2004; Jeon 2014; Li 2012; Moseley 2004; Moseley 2006; Moseley 2009; Mucha 1992; Oerlemans 1999), 11 trials (Aydemir 2006; Benedetti 2018; Bilgili 2016; Büyükturan 2018; Devrimsel 2015; Hazneci 2005; Hwang 2014; Lewis 2021; Sarkar 2017; Topcuoglu 2015; Vural 2016), and 10 trials (Askin 2014; Dimitrijevic 2014; Halicka 2021; Moseley 2005; Ozcan 2019; Ryan 2017; Saha 2021; Schreuders 2014; Strauss 2021; Uher 2000), respectively as being at 'low', 'unclear' and 'high' risk of attrition bias as a consequence of their adopted method of analysis.

Selective reporting

Seventeen trials either adequately reported outcome data (Askin 2014; Aydemir 2006; Benedetti 2018; Bilgili 2016; Büyükturan 2018; Cacchio 2009a; Devrimsel 2015; Dimitrijevic 2014; Duman 2009; Hazneci 2005; Li 2012; Moseley 2006; Saha 2021), or the authors supplied missing data (Halicka 2021; Ryan 2017; Sarkar 2017; Strauss 2021), and we judged them as being at low risk of reporting bias. We judged reporting bias to be unclear in one trial (Barnhoorn 2015). We judged a total of 16 trials as being at high risk of reporting bias; nine trials because of inadequate or incomplete reporting of primary outcomes, or both (den Hollander 2016; Durmus 2004; Hwang 2014; Jeon 2014; Oerlemans 1999; Ozcan 2019; Topcuoglu 2015; Uher 2000; Vural 2016), and seven trials because the trial authors presented data in graphical format only, i.e. point estimates with measures of variance were not reported (Cacchio 2009b; Lewis 2021; Moseley 2004; Moseley 2005; Moseley 2009; Mucha 1992; Schreuders 2014).

Sample size

None of the included trials had intervention arms with 200 or more participants per treatment arm. One trial randomised 60 participants to each trial arm and we judged it as being at unclear risk of bias (Li 2012). The remaining 33 trials had fewer than 50 participants per trial arm and we judged them as being at high risk of bias.

Duration of follow-up

Ten trials employed a follow-up period of eight or more weeks and we judged them as being at low risk of bias (Barnhoorn 2015; Cacchio 2009a; den Hollander 2016; Duman 2009; Halicka 2021; Li 2012; Moseley 2005; Moseley 2006; Oerlemans 1999; Ryan 2017). Five trials reported a follow-up period of two to seven weeks (Aydemir 2006; Benedetti 2018; Moseley 2004; Saha 2021; Schreuders 2014), and we judged these as being at unclear risk of bias. Nineteen trials employed a follow-up period of less than two weeks and we judged them as being at high risk of bias based on this criterion (Askin 2014; Bilgili 2016; Büyükturan 2018; Cacchio 2009b; Devrimsel 2015; Dimitrijevic 2014; Durmus 2004; Hazneci 2005; Hwang 2014; Jeon 2014; Lewis 2021; Moseley 2009; Mucha 1992; Ozcan 2019; Sarkar 2017; Strauss 2021; Topcuoglu 2015; Uher 2000; Vural 2016).

Other potential sources of bias

We considered four trials to be at high risk of other potential sources of bias: one trial because of differences in descriptions of the trial design and specification of a primary outcome measure between the trial registration and the published trial report (Strauss 2021); one trial because of imbalanced numbers of participants in an already very small group (n = 8) and differences in engagement with a co-intervention between groups (Ryan 2017); one trial because it did not report the baseline data of three participants excluded from the analysis and because of a likely highly significant baseline imbalance in duration of symptoms between groups (Schreuders 2014); and one trial because violations of the random sequence generation were permitted (Oerlemans 1999). We judged six trials to be at unclear risk of bias: one trial because 27% of patients switched between intervention arms (Barnhoorn 2015); one trial because it was published as a 'Letter to the Editor' and not as a full trial report (Cacchio 2009b); one trial because of baseline imbalances between groups with respect to gender and

duration of pain (Hwang 2014); one trial because it did not report participants' baseline pain data (Jeon 2014); one trial because of uncertainty regarding the extent to which a carry-over effect may have introduced bias in estimates of treatment effect (Moseley 2009); and one because it did not report participants' baseline demographics and characteristics (Sarkar 2017). The 23 other trials appeared to be free of other potential sources of bias.

Effects of interventions

See: **Summary of findings 1** Physiotherapy compared with minimal care for adults with CRPS I; **Summary of findings 2** Physiotherapy compared with minimal care for adults with CRPS II

See: Summary of findings 1 (Physiotherapy compared with minimal care for adults with CRPS I); Summary of findings 2 (Physiotherapy compared with minimal care for adults with CRPS II).

Physiotherapy versus occupational therapy or minimal care for CRPS I

One three-arm trial with 135 participants, which we judged as being at 'high' risk of bias based on a number of criteria, compared a physiotherapy programme (pain management advice, relaxation exercises, connective tissue massage, transcutaneous electrical nerve stimulation (TENS) and exercise) plus medical treatment according to a fixed pre-established protocol, to an occupational therapy programme (splinting, de-sensitisation, functional rehabilitation) plus medical management and to, what we understand is, an attention control intervention, described as 'social work' (SW) (which included attention, advice) plus medical management in participants with CRPS I of the upper limb secondary to mixed aetiologies (Oerlemans 1999). The trial authors did not adequately report details regarding the nature of the interventions and did not standardise the number of treatment sessions given with the intensity and frequency of treatment adjusted to the individual needs of participants. The trial authors did not report the overall duration of the treatment periods for each trial group.

Physiotherapy versus occupational therapy

Pain

Numerical data (i.e. group means and standard deviations (SD) for each time point) for the four self-reported measures of pain intensity (current pain, pain from effort of use of the affected extremity, least and worst pain experienced in the preceding week) were not reported and the trial authors have not provided these data. Consequently, no further analyses of these measures were possible and we could not determine effect sizes. However, according to the trial report there were no between-group differences in pain at 12-month follow-up (very low-certainty evidence).

Disability

Numerical data for measures of upper limb disability (Impairment Level Sum score, Radboud Skills Questionnaire, modified Greentest, Radboud Dexterity Test) were not reported and the trial authors have not provided these data. Consequently, no further analyses of these measures were possible and we could not determine effect sizes. However, according to the trial report there were no between-group differences in disability at 12-month follow-up (very low-certainty evidence).

Other outcomes

The trial authors did not report numerical data from other outcomes of interest, including measures of health-related quality of life (HRQoL) (Sickness Impact Profile) and adverse effects although the authors state that there were no between-group differences in well-being at 12 months follow-up (Oerlemans 1999) (very low-certainty evidence).

Certainty of the evidence

We judged the certainty of evidence for outcomes of pain and disability to be very low. We downgraded each three times, once for serious study limitations, once for inconsistency and once for imprecision. Consequently, we are uncertain whether a multimodal physiotherapy intervention improves disability or pain compared to an occupational therapy intervention in the treatment of CRPS I of the upper limb.

Physiotherapy versus minimal care

Pain

According to the trial authors (Oerlemans 1999), physiotherapy was superior to minimal care for reducing pain according to all four measures of pain intensity (current pain, pain from effort of use of the affected extremity, least and worst pain experienced in the preceding week) at three months post-recruitment, and for reducing pain from effort of use of the affected extremity at six months. However, there were no between-group differences for any measure of pain intensity at 12 months follow-up. Numerical data (i.e. group means and standard deviations (SD) for each time point) for the four self-reported measures of pain intensity were not reported, and the trial authors did not provide these data. Consequently, no further analyses of these measures were possible and we could not determine effect sizes (very low-certainty evidence).

Disability

Multimodal physiotherapy demonstrated a small between-group improvement in disability at 12 months follow-up compared to minimal care (Impairment Level Sum score, 5 to 50 scale (higher scores indicate greater disability); mean difference (MD) -3.7, 95% confidence interval (CI) -7.13 to -0.27, P = 0.03). Numerical data were not reported for other measures of disability (Radboud Skills Questionnaire, modified Greentest, Radboud Dexterity Test) or time points (six weeks, three months, six months), although the authors state that there were no between-group differences at 12 months follow-up (Oerlemans 1999) (very low-certainty evidence).

Other outcomes

The trial authors did not report data on other outcomes of interest, including HRQoL (Sickness Impact Profile) and adverse effects although the authors state that there were no between-group differences in HRQoL at 12 months follow-up (Oerlemans 1999) (very low-certainty evidence).

Certainty of the evidence

We judged the certainty of evidence for outcomes of pain and disability to be very low. We downgraded each three times, once for serious study limitations, once for inconsistency and once for imprecision. Consequently, we are uncertain whether a multimodal physiotherapy intervention improves disability or pain compared

to a social work (control) intervention in the treatment of CRPS I of the upper limb (Summary of findings 1).

Physiotherapy versus minimal care for CRPS II

No trials found (Summary of findings 2).

Upper limb aerobic exercise and physiotherapy versus physiotherapy alone

Topcuoglu 2015 (n = 40) compared aerobic upper limb exercise, using arm crank ergometry, combined with CRPS-specific (TENS, cold-packs, massage, contrast baths) and stroke-specific (various exercise approaches) physiotherapy to CRPS- and stroke-specific physiotherapy alone in participants with post-stroke upper limb CRPS I. We judged this trial as being at 'high' risk of bias on multiple domains.

Pain

The authors report between-group differences in favour of upper limb aerobic exercise for shoulder pain (10 cm visual analogue scale (VAS)) (daytime: MD -1.9, 95% CI -3.23 to -0.57; P < 0.005; on movement: MD -1.7, 95% CI -2.95 to -0.45 ; P < 0.007) and wrist pain (daytime: MD -1.75, 95% CI -2.87 to-0.63; P < 0.002; night-time: MD -1.3, 95% CI -2.48 to-0.12; P < 0.03, on movement: MD -2.05 95% CI -3.17 to -0.93 ; P < 0.003) immediately post-intervention. There was no further follow-up of participants. The trial authors did not report baseline numerical data for measures of pain intensity and they did not supply us with these data. Thus we were unable to perform any further analyses (very low-certainty evidence).

Disability

The trial authors did not report numerical data on disability.

Other outcomes

The trial authors did not report data on adverse effects or measure any other outcomes of interest.

Certainty of the evidence

We judged the certainty of evidence to be very low for pain, downgraded three times, once for serious study limitations, once for inconsistency and once for imprecision. Consequently, we are uncertain whether upper limb aerobic exercise combined with physiotherapy improves pain in the very short term compared to physiotherapy alone in people with post-stroke CRPS I.

Exposure-based interventions versus usual physiotherapy

Two trials investigated the effects of contrasting approaches of 'exposure'-based interventions (Barnhoorn 2015; den Hollander 2016). We did not pool trial data due to substantial differences in therapeutic rationale and the use of outcome measures for pain and function.

Pain exposure physical therapy versus usual physiotherapy

Barnhoorn 2015 compared the effect of 'Pain exposure physical therapy' (PEPT), whereby participants are directly exposed to painful movements and activities (through self-massage, 'forced' use during activities of daily living, progressive loading exercises, education) and are instructed to ignore the pain, to a conventional 'pain-contingent' approach (comprising of medication, mild exposure and exercise) in 56 participants with CRPS I of the upper or lower limb. The trial was at high risk of bias on multiple domains.

Pain

Barnhoorn 2015 reported that while both groups improved there was no clear evidence of a difference in pain intensity (1 to 10 VAS (higher scores indicating worse pain), MD 0.61, 95% CI -0.70 to 1.92) or in the trial's primary composite outcome measure of pain intensity, range of motion and skin temperature (Impairment Level Sum Score - Restricted Version (ISS-RV); 4 to 40 scale (higher scores indicate worse pain), MD 0.96, 95% CI -1.56 to 3.48) at nine-month follow-up (very low-certainty evidence).

Disability

There were no between-group differences in pain-related upper limb disability (Disability of the Arm, Shoulder and Hand; Dutch Language version (DASH-DLV); 0 to 100 scale (higher scores indicate greater disability), MD 6.47, 95% CI -5.97 to 18.90) or lower limb disability (Lower Limb Tasks Questionnaire; 0 to 40 scale (lower scores indicate greater disability), MD 5.11, 95% CI -0.45 to 10.68) at nine-month follow-up (very low-certainty evidence).

Other outcomes

There were no between-group differences in HRQoL (EuroQoL-5D index (EQ-5D); maximum 1 (higher scores indicate worse health), MD -0.01, 95% CI -0.10 to 0.08) at nine-month follow-up (very low-certainty evidence). The authors did not report data concerning adverse effects or measure any other outcomes of interest.

Certainty of the evidence

We judged the certainty of evidence for outcomes of pain, disability and HRQoL to be very low. We downgraded each three times, once for serious study limitations, once for inconsistency and once for imprecision. Consequently, we are uncertain whether a PEPT approach improves pain or disability compared to conventional treatment in people with CRPS I of the upper or lower limb.

Exposure in vivo versus usual physiotherapy

den Hollander 2016 compared the effect of an exposure intervention targeting pain-related fear avoidance compared to a 'protective pain-contingent' treatment as usual approach in 46 participants with CRPS I of the upper or lower limb and moderate to high pain-related fear. The trial had a high risk of bias secondary to a high dropout rate, some discrepancies in reported outcomes between their published protocol and the trial report, selective reporting of secondary outcomes and a small sample size.

Pain

The authors report additional between-group differences in favour of the exposure intervention, in reductions in pain intensity (Neuropathic Pain Scale; score range 0 to 10 (higher scores indicate worse pain)) post-treatment (MD -2.04 95% CI -3.01 to -1.07; P = 0.001) and at six-month follow-up (MD -2.82, 95% CI -4.18 to -1.46; P = 0.001), equating to a 36.7% (95% CI 19.2% to 54.1%) and 50.7% (95% CI 26.3% to 75.25%) reduction in baseline pain levels respectively, equivalent to 'moderately important change' and 'substantially important change' respectively (very low-certainty evidence).

Disability

den Hollander 2016 reported between-group differences in favour of the exposure intervention, in reductions of self-reported upper limb disability (Radboud Skills Questionnaire (RASQ), score range 0 to 5 (higher scores indicate greater disability)) post-treatment (MD -1.08, 95% CI -1.60 to -0.56; P = 0.001) and at six-month follow-up (MD -1.30, 95% CI -1.69 to -0.92 ; P = 0.001), and reductions in self-reported lower limb disability (Walking Ability Questionnaire (WAQ), score range 0 to 10 (higher scores indicate greater disability)) at six-month follow-up (MD -3.62, 95% CI -6.78 to -0.47; P = 0.02) but not at the post-treatment time point (very low-certainty evidence).

Other outcomes

The authors also report improvements in physical (SF36-PCS, score range 0 to 100 (lower scores indicate worse physical health)) and emotional HRQoL (SF36-MCS, score range 0 to 100 (lower scores indicate worse mental health)) at post-treatment (SF36-PCS: MD 25.93, 95% CI 15.92 to 35.91; P = 0.001; SF36-MCS: MD 16.23, 95% CI 6.85 to 25.63; P = 0.001) and six-month time points (SF36-PCS: MD 22.64, 95% CI 10.15 to 35.13; P = 0.001; SF36-MCS: MD 19.63, 95% CI 10.78 to 28.47; P = 0.001) in favour of the exposure intervention, equivalent to 64.9% (95% CI 39.8% to 89.9%), 29.9% (95% CI 11.1% to 42.5%), and 56.7% (95% CI 25.4% to 87.9%), 32.5% (95% CI 17.9% to 47.2%) consistent with a substantially important change in SF36-PCS score and a moderately important change in SF36-MCS score (very low-certainty evidence). The authors did not report data concerning adverse effects or measure any other outcomes of interest.

Certainty of the evidence

We judged the certainty of evidence for outcomes of pain, disability and HRQoL to be very low. We downgraded each three times, once for serious study limitations, once for inconsistency and once for imprecision. Consequently, we are uncertain whether an exposure in vivo approach targeting pain-related fear avoidance improves disability, pain or health-related quality of life compared to a conventional 'protective pain-contingent' treatment as usual approach in people with CRPS I of the upper or lower limb at short- and long-term follow-up.

Cortically directed sensory-motor rehabilitation strategies

Graded motor imagery (GMI)

We included five separate trials of GMI, all of which were small trials (13 to 37 participants) judged to be at 'high' risk of bias.

Graded motor imagery versus standard care

Two trials compared the same GMI protocol to control interventions of standard care (Moseley 2004; Moseley 2006) and one trial compared a different GMI protocol plus conventional treatment (occupational and therapy physiotherapy) to conventional treatment alone (Schreuders 2014).

Moseley 2004 (n = 13) compared a six-week GMI programme (consisting of two weeks of limb laterality recognition followed by two weeks of imagined movements followed by two weeks of mirror-box therapy) to 12 weeks of ongoing medical management and usual physiotherapy care in participants with longstanding CRPS I of the upper limb post wrist fracture. Moseley 2006 compared the same GMI programme to physical therapy and usual care in a combined cohort of 14 participants with phantom-limb pain and 37 participants with CRPS I of the upper or lower limb of mixed aetiologies. Schreuders 2014 (n = 18) compared a different six-week GMI programme (consisting of one week of limb laterality recognition, followed by one week of imagined movements, followed by four weeks of mirror-box therapy) plus conventional care (physiotherapy and occupational therapy) to conventional care alone in participants with longstanding CRPS I of the upper limb (aetiology not reported).

Pain

Moseley 2004 reported an improvement in pain intensity, as measured by the Neuropathic Pain Scale (NPS; score range 0 to 10 (higher scores indicate worse pain)) at six weeks post-treatment, in participants that received GMI compared to ongoing medical management. Moseley 2004 reported a number needed to treat (NNT) to obtain a 50% reduction in the NPS (total score) of three (95% CI 1.4 to 10.1). Moseley 2006 reported improvements in pain intensity, as measured by a 0 to 100 VAS (higher scores indicate worse pain) immediately post-intervention and at six months post-treatment for the combined cohort of participants with CRPS I and phantom limb pain. At six weeks post-treatment, Schreuders 2014 found no between-group differences on any measure of pain intensity (current, minimum or maximum over last three days).

Moseley 2004, Moseley 2006 and Schreuders 2014 presented data for changes in pain intensity graphically only and did not report numerical data (i.e. group means and standard deviation (SD) values at each time point) for measures of pain intensity. However, 0 to 100 VAS pain data at the post intervention time point were available from Moseley 2004 and the CRPS I participants in Moseley 2006 from a previous overview of systematic reviews of interventions for CRPS (O'Connell 2013). We used these data in this Cochrane Review with the authors' permission. Pooling of these results gave an effect size (mean difference) of -14.45 (95% CI -23.02 to -5.87; P = 0.001, 2 trials, 49 participants; Analysis 1.1) with no significant heterogeneity (I^2 = 29%). We expressed these data as a percentage of the mean baseline pain levels in the larger trial (58 out of 100), which equated to a 25% (95% CI 10% to 40%) reduction in baseline pain intensity at the end of the treatment period. Moseley 2004 presented outcomes at medium-term follow-up (six weeks post-treatment, n = 13, MD -20.00, 95% CI -32.13 to -7.97; P = 0.001). This equated to an improvement of 34% (95% CI 14% to 55%) of the baseline VAS pain level in the Moseley 2006 trial (average baseline data for pain VAS were not available from the Moseley 2004 trial report). At long-term follow-up (six months post-treatment (n = 36)) in Moseley 2006, the MD was -21.00, 95% CI -31.17 to -10.83; P < 0.001, which equates to an improvement of 36% (95% CI 19% to 54%). The immediate post-treatment effect was below the threshold for a moderately clinically important difference but exceeded the threshold for a minimally clinically important difference. The medium- and long-term effects met the threshold for a moderately important benefit (very low-certainty evidence). We were unable to obtain numerical data from Schreuders 2014.

Disability

Moseley 2006 reported improvements in disability, as measured by a 0 to 10 patient-specific functional scale (lower scores indicate greater disability), immediately post-intervention and at six months post-treatment for the combined cohort of participants with CRPS I and phantom limb pain. At six weeks post-treatment, Schreuders 2014 found no between-group differences

in function. Moseley 2006 and Schreuders 2014 presented data for changes in disability graphically only and did not report the numerical data (i.e. group means and SD values at each time point). We were unable to obtain numerical data from Schreuders 2014.

As described above, we were able to pool the data on disability from two trials (Moseley 2004 and Moseley 2006; data on CRPS I participants only), which returned a MD of 1.87 (95% CI 1.03 to 2.71; P < 0.001; I^2 = 41%; 2 trials, 49 participants; Analysis 1.2) at the end of treatment; 2.26 (95% CI 1.42 to 3.10; P < 0.001) at medium-term follow-up (Moseley 2004, n = 13); and 2.30 (95% CI 1.12 to 3.48; P < 0.001) at long-term follow-up (Moseley 2006, n = 36). This represented a large improvement in function from the baseline function score (0.5) in the control group of the larger trial (Moseley 2006) (very low-certainty evidence).

Other outcomes

None of these trials reported data about adverse effects or measured any other outcomes of interest.

Certainty of the evidence

We judged the certainty of evidence for pain and disability to be very low. We downgraded each three times, once for serious study limitations, once for inconsistency and once for imprecision. Consequently, we are uncertain whether GMI improves pain or disability compared to standard care for people with CRPS I of the upper limb post wrist fracture or CRPS I of the upper or lower limb of mixed aetiologies at short-, medium- or long-term follow-up.

Three graded motor imagery (GMI) protocols compared with each other

In a three-arm trial, Moseley 2005 (n = 20) compared a six-week GMI programme with its three components delivered in the 'correct' order (i.e. two weeks of laterality recognition followed by two weeks of imagined movements followed by two weeks of mirror-box therapy) to two other GMI programmes with selected components delivered in different orders at odds with its hypothesised mechanism of action, in participants with longstanding CRPS I of the upper limb post wrist fracture.

Pain

Improvements were found in pain intensity in the correctly ordered GMI group compared to both comparison groups, as measured by the NPS at 12 weeks post-treatment. Moseley 2005 reported that at 12-week follow-up, the mean reduction in NPS score for the correctly ordered GMI group was approximately seven and 18 points greater than the mean reductions in the other two groups respectively. The trial did not report numerical data for the outcome of pain intensity and we have been unable to obtain these data from the trial author. Consequently we were unable to perform any further analyses of these measures and we could not determine the effect sizes (very low-certainty evidence).

Disability

Improvements were found in function in the correctly ordered GMI group compared to both comparison groups, as measured by an 11-point NRS at 12 weeks post-treatment. The trial did not report numerical data for the outcome of function, and we have been unable to obtain these data from the trial author. Consequently we were unable to perform any further analyses of these measures and we could not determine the effect sizes (very low-certainty evidence).

Other outcomes

The trial did not report data concerning adverse effects and did not measure any other outcomes of interest.

Certainty of the evidence

We judged the certainty of evidence for pain and disability to be very low. We downgraded each three times, once for serious study limitations, once for inconsistency and once for imprecision. Consequently, we are uncertain whether appropriately ordered GMI was more effective at reducing pain and improving disability than inappropriately ordered GMI in people with longstanding CRPS I of the upper limb post wrist fracture.

Graded Motor Imagery versus waiting list control

One two-arm, two-period cross-over trial compared a GMI protocol (identical to that of Moseley 2004; Moseley 2006) to a waiting list control in 22 participants with CRPS II of mixed aetiologies (Strauss 2021). We judged this trial as being at 'high' risk of bias on multiple domains. In addition, there was no washout period to account for potential carry-over effects, in particular for those people who underwent the wait-list control intervention after undergoing GMI.

Pain

According to our analyses of the missing outcome data supplied to us by the trial authors, there was no clear evidence of a difference in pain at rest (0 to 10 cm VAS (higher scores indicating more severe pain), MD –0.58, 95% CI –1.94 to 0.78) or pain on movement (0 to 10 cm VAS (higher scores indicating more severe pain), MD –0.7, 95% CI –2.29 to 0.89) (very low-certainty evidence).

Disability

The trial authors did not measure disability.

Other outcomes

The trial authors did not report numerical data on adverse effects or measure any other outcomes of interest, and they were not able to complete follow-up measures of participants' CRPS severity scores, which requires investigator-assessed items, secondary to coronavirus restrictions during the trial. The authors responded to our request for data and reported to us that two participants reported a feeling of swelling of the affected limb during training, 12 participants reported increased pain during the training procedure, and two participants had increased pain levels after completing training.

Certainty of the evidence

We judged the certainty of evidence for pain and adverse effects to be very low. We downgraded each three times, once for serious study limitations, once for inconsistency and once for imprecision. Consequently, we are uncertain whether a six-week GMI rehabilitation programme improves pain in the very short term compared to a waiting-list control in people with CRPS II.

Mirror therapy

We included five trials of mirror therapy, four of which included participants with post-stroke CRPS I of the upper limb (Cacchio

2009a; Cacchio 2009b; Saha 2021; Vural 2016). The type and cause of CRPS was not reported in the other trial (Sarkar 2017).

Mirror therapy plus conventional stroke rehabilitation versus placebo mirror therapy plus conventional stroke rehabilitation

Cacchio 2009a (n = 48) compared four weeks of mirror therapy plus conventional stroke rehabilitation to placebo mirror therapy (covered mirror) plus conventional stroke rehabilitation in participants with CRPS I of the upper limb post-stroke in a trial judged to be at 'unclear' risk of bias.

Pain

Cacchio 2009a reported improvements in pain intensity and disability, at all post-treatment time points, in the mirror therapy group compared to the placebo group. Specifically, Cacchio 2009a reported a mean between-group difference following treatment in pain at rest (0 to 10 VAS (higher scores indicate worse pain)) of -2.9 (95% CI -4.23 to -1.57; P < 0.001) and in pain on movement (shoulder flexion) of -3.10 (95% CI -4.28 to -1.92; P < 0.001). At six-month follow-up the differences were still present, -3.4 (95% CI -4.71 to -2.09; P < 0.001) for pain at rest, and -3.8 (95% CI -4.96 to -2.64; P < 0.001) for pain on movement. The post-treatment and six-month follow-up mean differences for pain at rest equated to a 38% (95% CI 21% to 56%) and 45% (95% CI 28% to 62%) reduction in the average baseline pain level respectively, whilst the post-treatment and six-month follow-up mean differences for pain on movement equated to a 36% (95% CI 23% to 50%) and 45% (95% CI 31% to 58%) reduction in the average baseline pain level respectively, consistent with a moderately important benefit (very low-certainty evidence).

Disability

Regarding disability, Cacchio 2009a also reported between-group differences in functional limitation, in favour of mirror therapy, as measured by the functional ability subscale of the Wolf Motor Function Test (WMFT, 0 to 5 score range (higher scores indicate greater disability)) of -1.9 (95% CI -2.36 to -1.44, P < 0.001) at the end of treatment and of -2.3 (95% CI -2.88 to -1.72, P < 0.001) at six-month follow-up (very low-certainty evidence).

Other outcomes

The trial authors did not report data concerning adverse effects or measure any other outcomes of interest.

Certainty of the evidence

We judged the certainty of evidence for pain and disability to be very low. We downgraded each three times, once for serious study limitations, once for inconsistency and once for imprecision. Consequently, we are uncertain whether mirror therapy plus conventional stroke rehabilitation is more effective at reducing pain and improving disability compared to placebo mirror therapy plus conventional stroke rehabilitation in people with post-stroke CRPS I of the upper limb.

Mirror therapy versus placebo mirror therapy

In a separate three-arm trial, judged to be at 'high' risk of bias, Cacchio 2009b (n = 24) compared four weeks of mirror therapy (n = 8) to placebo mirror therapy (covered mirror) (n = 8) in participants with CRPS I of the upper limb post stroke.

Pain

Cacchio 2009b reported that seven out of eight participants in the mirror therapy group reported reduced pain (100 mm VAS; higher scores indicate worse pain) (median change in 0 to 100 VAS of -51 mm, range -70 to -18) compared with one of eight participants in the placebo mirror therapy group. The median change was not reported for the placebo mirror groups. At the end of the treatment period, pain scores were lower in the mirror therapy group compared to the placebo mirror groups. However, the trial authors did not report any further between-group data and we were unable to obtain these data from the trial authors. Consequently we were unable to perform any further analyses of these measures and we could not determine the effect size (very low-certainty evidence).

Disability

The trial authors did not report data on disability.

Other outcomes

The trial authors did not report data concerning adverse effects or measure any other outcomes of interest.

Certainty of the evidence

We judged the certainty of evidence for pain to be very low. We downgraded three times, once for serious study limitations, once for inconsistency and once for imprecision. Consequently, we are uncertain whether mirror therapy is more effective at reducing pain compared to placebo mirror therapy in people with post-stroke CRPS I of the upper limb.

Mirror therapy versus mental imagery

In the same trial (Cacchio 2009b) (n = 24), the effect of four weeks of mirror therapy (n = 8) was also compared to four weeks of mental imagery training (n = 8) in participants with CRPS I of the upper limb post stroke.

Pain

Cacchio 2009b reported that seven out of eight participants in the mirror therapy group reported reduced pain on movement (median change in zero to 100 VAS of -51 mm, range -70 to -18) compared with two of eight participants in the mental imagery group. The median change was not reported for the mental imagery group. At the end of the treatment period, pain scores were significantly lower in the mirror therapy group compared to the mental imagery group. However, the trial authors did not report any further between-group data and we were unable to obtain these data from the trial authors. Consequently we were unable to perform any further analyses of these measures and we could not determine the effect size (very low-certainty evidence).

Disability

The trial authors did not report data on disability.

Other outcomes

The trial authors did not report data concerning adverse effects or measure any other outcomes of interest.

Certainty of the evidence

We judged the certainty of evidence for pain to be very low. We downgraded three times, once for serious study limitations, once

for inconsistency and once for imprecision. Consequently, we are uncertain whether mirror therapy was more effective at reducing pain compared to mental imagery in people with post-stroke CRPS I of the upper limb.

Mirror therapy plus conventional stroke rehabilitation versus conventional stroke rehabilitation

Two trials investigated the effectiveness of mirror therapy plus conventional stroke rehabilitation compared to conventional stroke rehabilitation alone (Saha 2021; Vural 2016).

Saha 2021 (n = 38) and Vural 2016 (n = 30) both compared four weeks of mirror therapy plus conventional stroke rehabilitation to four weeks of patient-specific conventional stroke rehabilitation alone in participants with post-stroke CRPS I of the upper limb. We judged both trials to be at high risk of bias across a number of key domains.

Pain

Saha 2021 reported improvements in pain intensity (0 to 10 numerical rating scale (NRS), higher scores indicating worse pain) in favour of the combined mirror therapy/conventional stroke rehabilitation group compared to the conventional stroke rehabilitation alone group at the post-intervention (MD -1.40, 95% CI -2.26 to -0.54; P < 0.001) and two-week (MD -1.86, 95% CI -2.77 to -0.95; P < 0.001) follow-up time points, equating to a 22.1% (95% CI 8.5% to 35.6%) and 29.3% (95% CI 15.0% to 43.7%) reduction in the average baseline pain level respectively, consistent with minimal clinically important benefits, with the improvement at two weeks falling just short of our threshold for a moderate clinical benefit (very low-certainty evidence).

According to Vural 2016, improvements in pain intensity (0 to 10 VAS; higher scores indicate worse pain) were greater in the mirror therapy group (median within-group change of three points) compared to the control group (median within-group change of one point). The authors did not report mean values with measures of variance and in response to our request reported that they were unable to supply these missing data. Consequently we were unable to perform any further analyses of these measures and we could not determine additional estimates of effect sizes (very low-certainty evidence).

Disability

Saha 2021 reported improvements in disability (Functional Independence Measure, scoring properties and interpretation assumed to follow standardised methods, i.e. 18 to 126 scale, with lower scores indicating greater disability) in favour of the combined mirror therapy/conventional stroke rehabilitation group compared to the conventional stroke rehabilitation alone group at the post-intervention (MD 21.95, 95% CI 9.71 to 34.19; P < 0.001) and two-week (MD 25.82, 95% CI 14.12 to 37.52; P < 0.001) follow-up time points equating to a 32.4% (95% CI 14.3% to 50.5%) and 38.2% (95% CI 20.9% to 55.4%) improvement in the average baseline disability, consistent with a 'moderate' clinically important benefit (very low-certainty evidence).

According to Vural 2016, improvements in wrist (Fugl-Meyer Assessment (FMA); FMA-Wrist, score range 0 to 10 (lower scores indicate greater disability)) and hand (FMA-Hand, score range 0 to 14 (lower scores indicate greater disability)) scores were greater in the mirror therapy group (FMA-Wrist: median within-group change of 3 points; FMA-Hand: median within-group change of 3 points) compared to the control group (FMA-Wrist: median within-group change of 0 points; FMA-Hand: median within-group change of 0 points) (mean values and measures of variation not reported) (very low-certainty evidence).

Other outcomes

Saha 2021 and Vural 2016 did not report data concerning adverse effects or measure any other outcomes of interest.

Certainty of the evidence

We judged the certainty of evidence for pain and disability to be very low. We downgraded three times, twice for serious study limitations and once for imprecision. Consequently, we are uncertain whether mirror therapy combined with conventional stroke rehabilitation was more effective at reducing pain or improving disability compared to conventional stroke rehabilitation alone in people with post-stroke CRPS I of the upper limb.

Mirror visual feedback plus medical management versus contrast baths plus medical management

In a three-arm trial, Sarkar 2017 compared the effect of four weeks of mirror visual feedback (MVF) plus 900 mg/day gabapentin and 10 mg/day amitriptyline (n = 10) to a control group receiving the same pharmacological treatment plus contrast baths of the affected limb (n = 10) in participants with upper or lower limb CRPS but whose type and cause of CRPS was not reported. The trial was at high risk of bias across multiple domains.

Pain

The authors reported an improvement in both pain at rest (NRS 0 to 10; higher scores indicate worse pain) and pain on movement (NRS 0 to 10) in the MVF group compared to the contrast bath group. The authors supplied missing data, confirmed there were no dropouts and were followed up to the point of intervention completion only. According to our analyses there was a mean difference of -2.65 (95% CI -3.14 to -2.16; P < 0.001) in pain at rest in favour of the MVF group compared to the contrast bath group at the post-intervention time point, equating to a 53% (95% CI 43.2% to 62.8%) reduction in baseline pain levels, equivalent to 'substantially important change'. There were similar favourable mean differences for pain on movement in the MVF group compared to the contrast bath group (MD -3.15, 95% CI -3.78 to -2.52; P < 0.001) at the post-intervention time point, equating to a 40% (95% CI 32.0% to 48.0%) reduction in baseline pain levels, equivalent to 'moderately important change' (very low-certainty evidence).

Disability

The trial authors did not measure disability.

Other outcomes

The trial authors did not report data concerning adverse effects or measure any other outcomes of interest.

Certainty of the evidence

We judged the certainty of evidence for pain to be very low. We downgraded three times, once for serious study limitations, once for inconsistency and once for imprecision. Consequently, we are uncertain whether MVF combined with medical management

was more effective at reducing pain compared to contrast baths combined with medical management in the treatment of CRPS.

Mirror visual feedback plus medical management versus contrast baths and exercise plus medical management

In the same trial the effect of four weeks of mirror visual feedback plus 900 mg/day gabapentin and 10 mg/day amitriptyline (n = 10) was also compared to another control group receiving the same pharmacological treatment plus contrast baths and exercise (n = 10) (Sarkar 2017).

Pain

The authors reported a significant improvement in both pain at rest (NRS 0 to 10) and pain on movement (NRS 0 to 10) in the mirror visual feedback compared to the contrast bath and exercise group. According to our analyses there was a mean difference of -2.60 (95% CI -3.08 to -2.12; P < 0.001) in pain at rest in favour of the mirror visual feedback group compared to the contrast bath and exercise group at the post-intervention time point, equating to a 52% (95% CI 42.4% to 61.6%) reduction in baseline pain levels, equivalent to 'substantially important change'. There were similar favourable mean differences for pain on movement in the mirror visual feedback group compared to the contrast bath and exercise group (MD -3.25, 95% CI -3.70 to -2.80; P < 0.001) at the post-intervention time point, equating to a 41.2% (95% CI 35.5% to 47.0%) reduction in baseline pain levels, equivalent to 'moderately important change' (very low-certainty evidence).

Disability

The trial authors did not measure disability.

Other outcomes

The trial authors did not report data concerning adverse effects or measure any other outcomes of interest.

Certainty of the evidence

We judged the certainty of evidence for pain to be very low. We downgraded three times, once for serious study limitations, once for inconsistency and once for imprecision. Consequently, we are uncertain whether MVF combined with medical management was more effective at reducing pain compared to contrast baths and exercise combined with medical management in the treatment of CRPS.

Virtual body swapping

We included two trials of virtual body swapping, which is a method of evoking the perceptual illusion that a virtual body is perceived as one's own body, with mental rehearsal (Hwang 2014; Jeon 2014), and may be thought of as conceptually similar to mirror therapy.

Virtual body swapping with mental rehearsal versus 'watching movement only' (control)

In a three-arm trial, Hwang 2014 compared a single session of virtual body swapping with mental rehearsal (n = 13) to a ‘watching movement only’ control group (n = 13) in patients with CRPS types I and II of the upper or lower limb. Data regarding the number of participants with CRPS types I and II either in total or per group were not reported. Participants were followed up immediately post-treatment only. We rated the trial as at high risk of bias for selective outcome reporting and unclear risk of bias for multiple domains, including for random sequence generation and allocation concealment.

Pain

Pain intensity was measured with respect to the 'past week' and 'present'. Hwang 2014 reported that there were no between-group differences in changes in pain intensity (11-point Likert scale; higher scores indicate worse pain) but did not specify to which time point this referred to. Published data suggest that pain intensity was unchanged in the virtual body swapping with mental rehearsal group and worsened slightly in the 'watching movement only' control group. The authors did not reply to our requests for missing data. As a result, we could not conduct any further analyses (very low-certainty evidence).

Disability

The trial authors did not measure disability.

Other outcomes

The trial authors did not report data concerning adverse effects or measure any other outcomes of interest.

Certainty of the evidence

We judged the certainty of evidence for pain to be very low. We downgraded three times, once for serious study limitations, once for inconsistency and once for imprecision. Consequently, we are uncertain of the immediate effect of a single session of virtual body swapping with mental rehearsal compared to a ‘watching movement only’ control intervention in the treatment of CRPS.

Virtual body swapping with mental rehearsal versus mental rehearsal only (control)

In the same trial the effect of a single session of virtual body swapping with mental rehearsal (n = 13) was also compared to a ‘mental rehearsal only’ (n = 13) control group (Hwang 2014).

Pain

Hwang 2014 reported that there were no between-group differences in changes in pain intensity. Published data suggest that pain intensity was unchanged in the virtual body swapping with mental rehearsal group and worsened slightly in the mental rehearsal only control group. The authors did not reply to our requests for missing data. As a result, we could not conduct any further analyses (very low-certainty evidence).

Disability

The trial authors did not measure disability.

Other outcomes

The trial authors did not report data concerning adverse effects or measure any other outcomes of interest.

Certainty of the evidence

We judged the certainty of evidence for pain to be very low. We downgraded three times, once for serious study limitations, once for inconsistency and once for imprecision. Consequently, we are uncertain of the immediate effect of a single session of virtual body swapping with mental rehearsal compared to a mental rehearsal control intervention in the treatment of CRPS.

Virtual body swapping with mental rehearsal versus virtual body swapping alone

Jeon 2014 compared a single session of virtual body swapping with mental rehearsal compared to virtual body swapping alone in a total of 10 participants (number per group not reported) with CRPS I of either the upper or lower limbs, multiple limbs or the whole body, the aetiology of which was not reported. Participants underwent a single session of their allocated intervention with follow-up immediately post-treatment only. We rated the trial as at 'unclear' risk of bias for random sequence generation and allocation concealment, and at 'high' risk of bias for selective outcome reporting.

Pain

Jeon 2014 reported that there was no difference between the groups regarding pain intensity, as measured by an 11-point Likert rating scale ranging from zero (no pain) to 10 (severe pain) immediately post-treatment. The trial authors did not report numerical data for measures of pain intensity, and we have been unable to obtain these data from the trial authors. As a result, we could not conduct any further analyses and we could not determine the effect size (very low-certainty evidence).

Disability

The trial authors did not measure disability.

Other outcomes

The trial authors did not report data concerning adverse effects or measure any other any outcomes of interest.

Certainty of the evidence

We judged the certainty of evidence for pain to be very low. We downgraded three times, once for serious study limitations, once for inconsistency and once for imprecision. Consequently, we are uncertain of the immediate effect of a single session of virtual body swapping with mental rehearsal compared to virtual body swapping alone in the treatment of CRPS I.

Virtual reality versus sham virtual reality

One two-arm trial with 45 participants, which we judged as being at high risk of bias secondary to inadequate reporting of outcomes, its small sample size and short-term follow-up of participants, compared a virtual reality intervention (n = 23), during which participants visualised a digitally altered image of their affected hand, to a sham virtual reality intervention (n = 22) in participants with CRPS (type(s) not reported) of the upper limb (Lewis 2021).

Pain

Lewis 2021 reported a reduction in pain intensity (11-point NRS; higher scores indicate worse pain) in the virtual reality group compared to the sham virtual reality (MD 1.2; effect size SMD 0.7; with measures of variation either not explained or not reported) at the post-intervention time point. This equates to a 22% reduction in the average baseline pain level, consistent with a 'minimally important change'. The trial authors did not fully report numerical data for measures of pain intensity, and we have been unable to obtain these data from them. As a result, we could not conduct any further analyses or confirm the effect size (very low-certainty evidence).

Disability

The trial authors did not measure disability.

Other outcomes

The trial authors did not report data concerning adverse effects or measure any other outcomes of interest.

Certainty of the evidence

We judged the certainty of evidence for pain to be very low. We downgraded three times, once for serious study limitations, once for inconsistency and once for imprecision. Consequently, we are uncertain whether virtual reality is more effective at reducing pain compared to sham virtual reality in the treatment of CRPS.

Four tactile discrimination training protocols compared with each other

We included one trial that employed a within-subject, randomised, cross-over design, which compared four tactile discrimination training (TDT) protocols with one another (n = 10) in participants with CRPS I of the upper limb from mixed aetiologies (Moseley 2009).

Pain

Moseley 2009 reported that there were no differences in self-reported pain intensity (0 to 100 VAS; higher scores indicate worse pain) at two-day follow-up between the four TDT protocols. The trial authors did not report numerical data for measures of pain intensity, and they have not supplied us with these data. Thus we were unable to perform any further analyses and we could not determine the effect size. We rated the trial at 'high' risk of bias for selective outcome reporting, sample size and duration of follow-up (very low-certainty evidence).

Disability

The trial authors did not measure disability.

Other outcomes

Regarding adverse effects, three participants reported that the pressure stimuli associated with the TDT occasionally hurt but that this was not enough to necessitate modification or cessation of the TDT training (very low-certainty evidence). The trial authors did not measure any other outcomes of interest.

Certainty of the evidence

We judged the certainty of evidence for pain and adverse effects to be very low. We downgraded three times, once for serious study limitations, once for inconsistency and once for imprecision. Consequently, we are uncertain of the effects of TDT in people with CRPS I of the upper limb at short-term follow-up.

Prism adaptation treatment versus sham prism adaptation treatment

We included one trial that compared two weeks of twice-daily prism adaptation treatment, during which participants perform a pointing task while wearing adapted goggles in an attempt to counter-lateralise attention bias in attention and spatial representations, with a sham prism adaptation treatment in 49 participants with upper limb CRPS I (Halicka 2021). We judged the trial as being at high risk of bias secondary to a small sample

size and high risk of attrition bias secondary to violation of the intention-to-treat principle and a high dropout rate at six-month follow-up, however we note that the primary endpoint was immediately post-intervention.

Pain

Halicka 2021 found no clear evidence of benefit of prism adaptation treatment beyond sham for treating the primary outcomes of pain (11-point NRS; higher scores indicate worse pain) at short- or long-term follow-up (mean differences and 95% CI not reported) (very low-certainty evidence).

Disability

The trial authors did not measure disability.

Other outcomes

There was no clear evidence of a difference in Patient's Global Impression of Change (1 to 7 scale; lower scores indicate poorer treatment outcomes) at short- or long-term follow-up (differences in medians with measure of variation not reported) (very low-certainty evidence). The trial authors did not report data concerning adverse effects or measure other outcomes of interest.

Certainty of the evidence

We judged the certainty of evidence for pain and Patient's Global Impression of Change to be very low. We downgraded three times, once for serious study limitations, once for inconsistency and once for imprecision. Consequently, we are uncertain of the effects of prism adaptation treatment in people with CRPS I of the upper limb at short-term follow-up.

Electrophysical agents

Ultrasound of the stellate ganglion versus sham ultrasound of the stellate ganglion

One three-arm trial (n = 45) compared two different doses (3.0 watts and 0.5 watts intensity) of high-frequency ultrasound to sham ultrasound (Askin 2014). All trial groups also received multimodal conventional treatment that included a course of medication (including vitamin C, gabapentin and prednisolone) and physiotherapy (including TENS, contrast baths, active and passive range of motion exercises and stretching, resistance and mirror box exercises). The participants received treatments daily for 20 days. The trial was small with fewer than 50 participants, and we judged it to be at 'high' or 'unclear' risk of bias based on a number of criteria.

Pain

There was no clear evidence of a difference in pain intensity (10 cm VAS; higher scores indicate worse pain) at the post-intervention time point and there was no further follow-up (mean differences with measures of variation not reported) (very low-certainty evidence).

Disability

There was no clear evidence of a difference in disability (DASH (Turkish language version); score range not reported, higher scores indicating greater disability) at the post-intervention time point and there was no further follow-up (mean differences with measures of variation not reported) (very low-certainty evidence).

Other outcomes

The trial authors did not report data concerning adverse effects or measure any other outcomes of interest.

Certainty of the evidence

We judged the certainty of evidence for pain and disability to be very low. We downgraded three times, once for serious study limitations, once for inconsistency and once for imprecision. Consequently, we are uncertain of the effects of ultrasound to the stellate ganglion compared to a sham intervention in people with CRPS I of the upper limb at short-term follow-up.

Stellate ganglion block (SGB) with lidocaine versus SGB with ultrasound versus sham SGB with lidocaine and ultrasound

One three-arm trial (n = 25) compared stellate ganglion block with lidocaine to blocks with ultrasound and placebo conditions for both interventions. All trial groups received exercises, TENS, contrast baths, compression and oral paracetamol. We judged the trial to be at 'high' or 'unclear' risk of bias based on a number of criteria (Aydemir 2006).

Pain

There was no clear evidence of a difference in pain intensity (0 to 10 VAS; higher scores indicate worse pain) at the post-intervention (MD 0.08, 95% CI -2.11 to 2.27) or one-month follow-up time points (MD 0.00, 95% CI -1.69 to 1.69) (very low-certainty evidence).

Disability

Aydemir 2006 measured hand disability using a Functional Hand Scale (0 to 19 scale, higher scores indicating greater disability) and reported improvements in all three trial groups post-treatment and at one-month follow-up. According to our analyses there were greater improvements in the placebo group post-treatment (MD -7.86, 95% CI -14.33 to 1.39) and at one-month follow-up (MD 6.79, 95% CI 1.19 to 12.34) compared to the SGB with ultrasound group only (very low-certainty evidence).

Other outcomes

The trial authors did not report data concerning adverse effects or measure any other outcomes of interest.

Certainty of the evidence

We judged the certainty of evidence for pain and disability to be very low. We downgraded three times, once for serious study limitations, once for inconsistency and once for imprecision. Consequently, we are uncertain of the effects of SGB with lidocaine or ultrasound compared to a sham intervention in people with CRPS I of the upper limb at short-term or one-month follow-up.

Ultrasound of the stellate ganglion versus TENS

One trial with 30 participants compared ultrasound of the stellate ganglion to TENS in military recruits with acute (mean duration of symptoms: 44 days) CRPS I of the upper limb secondary to mixed aetiologies (Hazneci 2005). Both groups also received contrast baths and physiotherapist-prescribed exercises. We judged the trial to be at 'unclear' risk of bias for random sequence generation and allocation concealment.

Pain

In this trial the ultrasound group demonstrated inferior post-treatment pain scores (0 to 10 VAS (higher scores indicate worse pain), MD 2.13, 95% CI 1.47 to 2.79, P < 0.001), which equates to a potentially clinically important difference of 27% (95% CI 19% to 36%) of the average baseline pain score (very low-certainty evidence). The trial authors measured pain intensity at the end of the three-week intervention period only without longer-term follow-up.

Disability

The trial authors did not measure disability.

Other outcomes

The trial authors did not report data concerning adverse effects or measure any other outcomes of interest.

Certainty of the evidence

We judged the certainty of evidence for pain to be very low. We downgraded three times, once for serious study limitations, once for inconsistency and once for imprecision. Consequently, we are uncertain of the effects of ultrasound of the stellate ganglion compared to TENS in people with acute CRPS I of the upper limb.

(Pulsed) electromagnetic field therapy (PEMF) versus placebo PEMF

Three trials investigated the effectiveness of pulsed electromagnetic field therapy (Durmus 2004; Benedetti 2018; Büyükturan 2018). One trial with 40 participants compared pulsed electromagnetic field (PEMF) treatment (100 Gauss, 50 Hz, five times weekly for six weeks) plus calcitonin and a stretching exercise routine to placebo PEMF plus calcitonin and stretching in participants with acute (mean duration of symptoms: 52 days) CRPS I of the upper limb following Colles' fracture (Durmus 2004). We rated the trial at 'high' risk of bias for selective outcome reporting, study size and duration of follow-up and at 'unclear' risk of bias for allocation concealment. Benedetti 2018 (n = 30) compared 10 sessions of PEMF and physiotherapy (education, psychological support, mobilisation, exercise, desensitisation, proprioceptive feedback, gait rehabilitation or occupational therapy as needed) to sham PEMF and physiotherapy in patients with upper and lower limb CRPS I of mixed aetiologies. We judged the trial to be at 'unclear' risk of bias overall secondary to uncertainties concerning their method of allocation concealment and whether or not they employed the 'intention-to-treat' principle. The trial was at high risk of bias given the small sample size. Büyükturan 2018 (n = 42) compared the effectiveness of 30 sessions of electromagnetic field therapy (EMFT) and physiotherapy (stretching, range of motion exercises) to placebo EMFT and physiotherapy in patients with upper limb CRPS I. We judged the trial to be at high risk of selection bias secondary to the use of a pseudo-randomisation procedure, the small sample size and follow-up limited to the post-intervention point only.

Pain

At the end of treatment, Durmus 2004 found no clear evidence of a difference in pain intensity (10 cm VAS; higher scores indicate worse pain) at rest or on activity (null effect size data could not be estimated because the authors did not report the number of participants in each group). Benedetti 2018 reported improvements in pain intensity (10 cm VAS; higher scores indicate worse pain) in favour of the PEMF group compared to sham at the post-intervention (MD -2.2, 95% CI -2.41 to -1.99; P < 0.001) and one-month (MD -2.5, 95% CI -2.79 to -2.21; P < 0.001) follow-up time points equating to a 46.3% (95% CI 41.9% to 50.7%) and 52.6% (95% CI 46.5% to 58.7%) reduction in the average baseline pain level, consistent with a 'moderate' and 'substantial' clinically important benefits, respectively. Büyükturan 2018 found an improvement in pain intensity (average pain over the last week using a 10 cm VAS; higher scores indicate worse pain) in the EMFT compared to the placebo EMFT group at the post-intervention time point. According to our analyses there was a mean difference of -1.6 (95% CI -2.37 to -0.83; P < 0.001) in favour of the EMFT group compared to the placebo EMFT group, equating to a 29.1% (95% CI 15.1% to 43.1%) reduction in baseline pain levels, falling just short of the threshold of a 'moderately important change'. We were unable to pool the data from these trials secondary to reporting limitations (e.g. Durmus 2004 did not report the number of participants in each trial arm) and study heterogeneity (very low-certainty evidence).

Disability

Benedetti 2018 reported an improvement in a self-reported composite measure of lower limb pain/disability in the participants with lower limb CRPS I (n = 18) (Maryland Foot Score (MFS) 0 to 100) in favour of the PEMF group compared to sham at both post-intervention (MD 14.4, 95% CI 11.36 to 17.44; P < 0.001) and one-month (MD 14.9, 95% CI 11.34 to 18.46) time points equating to a 19.6% (95% CI 15.5% to 23.8%) and 20.3% (95% CI 15.4% to 25.1%) improvement in average baseline pain/disability, consistent with 'minimally' important change. There was no benefit from PEMF according to a self-reported composite measure of upper limb function/pain in the participants with upper limb CRPS I (n = 12) (Disabilities of the Arm, Shoulder, and Hand (DASH) 0 to 100), where there was in fact a significant improvement in favour of the sham PEMF group at both post-intervention (MD -14.0, 95% CI -23.59 to -4.41; P < 0.004) and one-month (MD -23.3, 95% CI -29.52 to -17.08) time points, equating to a 17.2% (95% CI 5.4% to 29.0%) and 28.6% (95% CI 21.0% to 36.3%) improvement in average baseline pain/disability, consistent with 'minimally' important change. Büyükturan 2018 found no clear evidence of a difference in disability (Quick Disabilities of the Arm, Shoulder and Hand (Q-DASH); 0 to 100 range; higher scores indicate greater disability; MD 2, 95% CI -3.91 to 7.91) at the post-intervention time point (very low-certainty evidence).

Other outcomes

Büyükturan 2018 and Durmus 2004 did not report data concerning adverse effects or measure other outcomes of interest. Benedetti 2018 reported that none of the participants presented with adverse effects (very low-certainty evidence) and they did not measure other outcomes of interest.

Certainty of the evidence

We judged the certainty of evidence for pain, disability and adverse effects to be very low. We downgraded three times, once for serious study limitations, once for inconsistency and once for imprecision. Consequently, we are uncertain of the effects of PEMF compared to placebo PEMF in the treatment of CRPS I.

Transcutaneous electrical nerve stimulation (TENS) versus sham TENS

Two trials investigated the effectiveness of TENS (Bilgili 2016; Ryan 2017). Bilgili 2016 compared 15 sessions of TENS plus conventional physiotherapy (contrast bath, whirlpool bath, exercise programme) to sham TENS plus physiotherapy in 30 participants with upper limb CRPS I. We rated the trial as being at high risk of bias across a number of key domains as well as secondary to a small sample size and follow-up limited to the post-intervention point only. Ryan 2017 compared (what we assume was) 21 sessions of TENS plus physiotherapy (advice, education, exercise, motor imagery, desensitisation, hydrotherapy) (n = 6) to sham TENS plus physiotherapy (n = 2) in a small-scale feasibility trial that included participants with CRPS I of the upper limb. The trial was at high risk of bias across a number of key domains as well as secondary to a small sample size. Given the particularly small sample size, violation of the intention-to-treat principle and the 50% dropout rate we did not undertake any further analyses of the missing data the authors supplied as we did not think it would be possible to derive any clinically meaningful effect estimates for pain and function outcomes.

Pain

There was no clear evidence of a difference in pain (100 mm VAS; higher scores indicating worse pain; MD -9.0, 95%CI -18.5 to 0.5, p=0.074) (Bilgili 2016) (very low-certainty evidence).

Disability

There was no clear evidence of a difference in hand disability (Duruöz Hand Index; scale scoring properties not adequately reported, higher scores indicate greater disability; MD -3.6, 95% CI -13.38 to 6.18) (Bilgili 2016) (very low-certainty evidence).

Other outcomes

The trial authors did not report data concerning adverse effects or measure any other outcomes of interest.

Certainty of the evidence

We judged the certainty of evidence for pain and disability to be very low. We downgraded three times, once for serious study limitations, once for inconsistency and once for imprecision. Consequently, we are uncertain of the effects of TENS on pain and disability compared to sham TENS in the treatment of CRPS I of the upper limb.

Laser therapy versus Interferential therapy

One trial with 50 participants compared 20 sessions of low-level laser therapy with interferential current therapy in participants with post-traumatic CRPS I of the upper or lower limb (Dimitrijevic 2014). Both trial groups also received kinesitherapy that consisted of individualised active and active assisted exercises, strictly dosed up to pain threshold. We rated the trial at 'high' risk of bias for incomplete outcome data, trial size and duration of follow-up.

Pain

Dimitrijevic 2014 reported an improvement in pain at rest (0 to 100 VAS) of -8.6 (95% CI -16.27 to -0.93, P = 0.03) in favour of laser therapy at the post-intervention time point. This equates to a difference of 14% (95% CI 1.5% to 26%) from the mean baseline pain score of the two groups, which falls below our criteria for a minimal clinically important difference. There was no clear evidence of a difference with respect to pain with movement of the affected wrist or ankle according to our analysis (MD 10.2, 95% CI 0.17 to 20.24) (very low-certainty evidence).

Disability

The trial authors did not measure disability.

Other outcomes

The trial authors reported that there were no adverse effects of therapy recorded (very low-certainty evidence). The trial authors did not measure other outcomes of interest.

Certainty of the evidence

We judged the certainty of evidence for pain and adverse effects to be very low. We downgraded three times, once for serious study limitations, once for inconsistency and once for imprecision. Consequently, we are uncertain of the effects of laser compared to interferential therapy in the treatment of CRPS I of the upper or lower limb.

CO_2 bath therapy and exercise versus exercise

One trial with 40 participants compared carbon dioxide (CO_2) baths in addition to exercise therapy with exercise therapy alone in participants with post-traumatic CRPS I of the hand (Mucha 1992). Neither intervention is clearly described in the paper though the baths were administered in 12-minute sessions five times a week for four weeks. We rated the study at 'high' risk of bias on five separate criteria.

Pain

Mucha 1992 reported that there was an improvement in pain at rest, pain with movement and night pain (measurement properties not described) in favour of the CO_2 bath group. The trial authors did not report numerical data, and we have been unable to obtain these data from the trial authors. Consequently, we were unable to perform any further analyses of these measures and could not determine an effect size (very low-certainty evidence).

Disability

The trial authors did not measure disability.

Other outcomes

The trial authors did not report data concerning adverse effects or measure any other outcomes of interest.

Certainty of the evidence

We judged the certainty of evidence for pain to be very low. We downgraded three times, once for serious study limitations, once for inconsistency and once for imprecision. Consequently, we are uncertain of the effects of CO_2 baths combined with exercise compared to exercise alone in the treatment of CRPS I of the hand.

Whirlpool baths versus neuromuscular electrical stimulation

Devrimsel 2015 (n = 60), compared the effects of 15 sessions of a whirlpool bath intervention to 15 sessions of neuromuscular electrical stimulation (NMES) in a two-arm trial of participants with upper limb CRPS I. Both groups also received underwater ultrasound and exercise therapies. We rated the trial as being at

'unclear' or 'low' risk of bias across all key domains, and at high risk of bias secondary to a small size and follow-up limited to the post-intervention point only.

Pain

Devrimsel 2015 reported improvements in pain intensity (10 cm VAS; higher scores indicate worse pain) favouring the whirlpool bath group at the post-intervention time point, although according to our analysis a MD of -0.65 (95% CI -1.03 to -0.27; P < 0.001), equating to a 9.8% (95% CI 4.1% to 15.6%) reduction in the average baseline level of pain is probably clinically unimportant (very low-certainty evidence).

Disability

The trial authors did not measure disability.

Other outcomes

The trial authors reported that none of the participants experienced any 'treatment-associated complications' (which we assume to mean adverse effects) (very low-certainty evidence) and they did not measure any other outcomes of interest.

Certainty of the evidence

We judged the certainty of evidence for pain and adverse effects to be very low. We downgraded three times, once for serious study limitations, once for inconsistency and once for imprecision. Consequently, we are uncertain of the effects of whirlpool baths compared to NMES in the treatment of CRPS I of the upper limb.

Fluidotherapy plus conventional stroke rehabilitation versus conventional stroke rehabilitation

Ozcan 2019 (n = 32) compared the effectiveness of 15 sessions of fluidotherapy, a dry heat modality, combined with conventional rehabilitation to conventional rehabilitation alone in participants with post-stroke upper limb CRPS I. The trial was at high risk of bias on multiple key domains and secondary to a small size and follow-up limited to the post-intervention point only.

Pain

Ozcan 2019 reported no clear evidence of a difference in pain intensity (10 cm VAS; higher scores indicate worse pain) at the post-intervention time point (mean scores with measures of variance not reported) (very low-certainty evidence).

Disability

There was no clear evidence of a difference in disability (Functional Independence Measure (FIM) motor items; 1 to 7 scale, lower scores indicate greater disability) at the post-intervention time point (mean scores with measures of variance not reported) (very low-certainty evidence).

Other outcomes

The trial authors did not report data concerning adverse effects or measure any other outcomes of interest.

Certainty of the evidence

We judged the certainty of evidence for pain and disability to be very low. We downgraded each three times, once for serious study limitations, once for inconsistency and once for imprecision. Consequently, we are uncertain of the effects of fluidotherapy combined with conventional rehabilitation compared to conventional rehabilitation alone in people with post-stroke upper limb CRPS I.

Other interventions

Manual lymphatic drainage (MLD) therapy versus conventional care

Two trials investigated the effectiveness of adding MLD therapy to rehabilitation (Duman 2009; Uher 2000). Duman 2009 (n = 34) compared the addition of MLD massage to conventional care (nonsteroidal anti-inflammatory drugs and physical therapy) to conventional care alone in participants with CRPS I of the upper limb of mixed aetiology. Uher 2000 (n = 40) compared the addition of MLD in addition to exercise therapy to exercise therapy alone in participants with CRPS I of the lower limb of mixed aetiology. We rated both trials as being at 'high' risk of bias on multiple criteria.

Pain

Both trials showed no clear evidence of an effect from the addition of MLD on pain intensity. We were unable to extract accurate data from either study and so no further analyses were possible (very low-certainty evidence).

Disability

The trial authors did not measure disability.

Other outcomes

The trial authors did not report data concerning adverse effects or measure any other outcomes of interest.

Certainty of the evidence

We judged the certainty of evidence for pain to be very low. We downgraded three times, once for serious study limitations, once for inconsistency and once for imprecision. Consequently, we are uncertain of the effects of MLD combined with conventional care compared to conventional care alone for the treatment of CRPS I.

Electro-acupuncture and massage versus rehabilitation

One trial (n = 120) compared 30 sessions of electro-acupuncture combined with upper limb massage therapy to 30 sessions of rehabilitation in participants with post-stroke shoulder-hand syndrome (Li 2012). Rehabilitation consisted of active-assisted scapular movements, Bobath exercises to clench the fist, functional transfer training and proprioceptive neuromuscular facilitation (PNF) exercise. We rated the trial at 'high' risk of bias for blinding of participants and at 'unclear' risk of bias for sample size.

Pain

Li 2012 reported greater reductions in pain intensity (in the shoulder when moved passively to 90°; measurement properties not reported) in favour of the electro-acupuncture and massage group at the end of the six-week treatment period (MD -1.70, 95% CI -2.09 to -1.31, P = 0.01), which were sustained at 12-week follow-up (MD -1.40, 95% CI -1.78 to -1.02, P < 0.001). The post-treatment and 12-week follow-up MD values equated to a 21% (95% CI 16% to 26%) and 18% (95% CI 13% to 22%) reduction in the average baseline pain level respectively. These were below the threshold for a moderately clinically important difference but the point estimates exceeded the IMMPACT threshold (15%) for a minimally important benefit (very low-certainty evidence).

Disability

Li 2012 reported no difference in hand disability (Fugl-Meyer evaluation of functional movement of the hand; 0 to 14 scale, lower scores indicate greater disability) between the two trial groups, but a difference in upper limb function (as measured by the Fugl-Meyer evaluation of functional movement of the upper limb; 0 to 66 score, lower scores indicate greater disability) in favour of the electro-acupuncture and massage group at the end of treatment (MD 4.5, 95% CI 0.85 to 8.15, P = 0.05) but not at the 12-week follow-up time point (very low-certainty evidence).

Other outcomes

The trial authors reported that there were no adverse effects associated with the interventions in either trial group. They did not measure any other outcomes of interest.

Certainty of the evidence

We judged the certainty of evidence for pain, disability and adverse effects to be very low. We downgraded each three times, once for serious study limitations, once for inconsistency and once for imprecision. Consequently, we are uncertain of the effects of electro-acupuncture combined with upper limb massage therapy compared to a stroke rehabilitation intervention for the treatment of post-stroke shoulder-hand syndrome. We also have some concerns regarding the diagnostic equivalence of 'shoulder-hand syndrome' and CRPS I and whether the control intervention was directed towards the management of the shoulder-hand syndrome explicitly or if it was a general rehabilitation programme aimed at addressing the impairments related to the stroke, both of which may have implications for the generalisability of this trial's findings.

DISCUSSION

Summary of main results

The evidence arising from the clinical trials included in this review is very uncertain. As such, we cannot draw any firm conclusions regarding the effectiveness or harmfulness of a broad range of physiotherapy interventions for treating the pain and disability associated with CRPS I in adults.

One included trial provided very low-certainty evidence that a multimodal physiotherapy programme may provide a small, long-term improvement in impairment compared to a minimal intervention of ‘social work’, but the magnitude of this effect is of questionable clinical significance. We could not determine its effect on a range of pain-related outcomes (Oerlemans 1999).

Two trials of cognitive-behavioural approaches that employed differing forms of exposure interventions, compared to a conventional 'pain-contingent' approach, provided contrasting evidence (Barnhoorn 2015; den Hollander 2016). One trial found that exposure through 'forced' limb use does not improve pain, functional disability or health-related quality of life in the medium- or longer-term (Barnhoorn 2015), while another found that 'graded' exposure targeting pain-related fear avoidance may provide 'moderate' to 'substantial' improvements in pain, disability and health-related quality of life at short- and long-term follow-up (den Hollander 2016). The difference in findings between these two 'exposure-based' interventions may reflect differences in their theoretical basis and therapeutic approach. In the approach used by Barnhoorn 2015 patients are directly exposed to painful activities and instructed to ignore the pain in order to attain their personal goals, whereas in the trial by den Hollander 2016 patients with moderate to high pain-related fear are repeatedly exposed to feared movements and activities in order to adjust their expectancies regarding the association of activities and increased pain, reduce their fear and subsequently their disability. But given the very low-certainty of this evidence further trials of 'exposure' based interventions are warranted.

Evidence that supports the use of cortically directed sensory-motor rehabilitation strategies was mixed. Our findings suggest that graded motor imagery (GMI) may provide clinically meaningful medium- and long-term improvements in both pain and disability in people with CRPS I and that mirror therapy may provide short- and possibly long-term clinically meaningful improvements in pain and function in people with CRPS I following stroke. We also identified one trial of mirror therapy that was terminated early secondary to difficulties in recruiting participants and an interim analysis of which found an apparent lack of treatment effect (NCT02667717). The effectiveness of mirror therapy in broader participant populations with CRPS I (e.g. post-trauma) remains unknown. The results from these trials were all from very low-certainty studies and were inconsistent, and so should be treated with caution.

We also found very low-certainty evidence that more novel interventions such as virtual body swapping with/without mental rehearsal (Hwang 2014; Jeon 2014), tactile discrimination training (TDT) (Moseley 2009), and prism adaptation treatment (Halicka 2021) do not provide any short-term benefits in pain for people with CRPS I, and that a virtual reality intervention may provide minimal clinically significant benefits in pain in the short term (Lewis 2021).

Trials that investigated the use of other physiotherapy interventions provide mixed results. Overall we found no clear evidence of clinical effectiveness for upper limb aerobic exercise, ultrasound over the stellate ganglion, pulsed electromagnetic field therapy, TENS, CO_2 bath therapy, fluidotherapy, and manual lymphatic drainage combined with and/or compared to either sham or other active interventions (very low-certainty evidence). Laser therapy, whirlpool baths and electro-acupuncture combined with massage may provide small clinically insignificant, short- to medium-term improvements in pain intensity compared to various active comparators in adults with CRPS I (very low-certainty evidence). We are generally uncertain of the effects of any of these interventions on pain and disability in adults with CRPS I. Details regarding adverse events were generally not reported.

Very low-certainty evidence indicates that manual lymphatic drainage (MLD) is not beneficial for pain in people with CRPS I compared to other active interventions (Duman 2009; Uher 2000).

We found very low-certainty evidence from one trial that electro-acupuncture and massage were superior to a stroke rehabilitation programme for pain on passive shoulder movement in shoulder-hand syndrome post stroke at longer-term follow-up. However, the magnitude of this effect was unlikely to be clinically important and both the reliability and validity of the outcome measure used are questionable (Li 2012).

Only five trial reports, four related to electrophysical modalities (Benedetti 2018; Devrimsel 2015; Dimitrijevic 2014; Ryan 2017), and

one to TDT (Moseley 2009), commented on the presence or absence of adverse effects and reported no serious effects.

We found only one trial that included people with CRPS II exclusively (Strauss 2021).

Overall, we identified a lack of high- or moderate-certainty evidence with which to inform or guide rehabilitation practice in people with CRPS I or II. Based on the current body of evidence, we cannot draw any accurate conclusions regarding the effectiveness or safety of any of the physiotherapy interventions identified in this Cochrane Review.

Overall completeness and applicability of evidence

The evidence base for the use of physiotherapy interventions in CRPS is incomplete, although this reflects a broader problem for all intervention research in CRPS (O'Connell 2013). Most included trials (29/34) used established diagnostic criteria to identify participants with CRPS I. However, as might be expected given the development history of such criteria in CRPS, there was some variation in the criteria used between included trials. Beyond various issues relating to risk of bias and study size (see Quality of the evidence) there are few instances where more than one included trial tested a specific intervention. Furthermore, 22 (65%) trials were single-centre trials and the number of trial sites was unreported in nine (26%) trials. Single-centre RCTs have been shown to exhibit larger treatment effects, and while the cause of this is unknown, authors and users of randomised controlled trials (RCTs), systematic reviews and meta-analyses should consider this when reporting and interpreting effect sizes (Bafeta 2012; Deschartes 2011; Unverzagt 2013). Two trials specifically recruited participants from military populations (Aydemir 2006; Hazneci 2005). As such, it is possible that contextual factors specific to that participant group and environment may limit the applicability of those results to civilian clinical practice. Eighteen trials (53%) measured outcomes immediately at the end of treatment only, with no longer-term follow-up, and 24 (71%) of the included trials followed up their participants for less than three months. Such trials offer limited information about the genuine clinical utility of interventions for a condition that is commonly persistent. The broad heterogeneity of interventions assessed in the included trials, together with the poor reporting of the interventions, afforded us limited opportunities to pool data.

The aim of this Cochrane Review was to investigate the effectiveness of physiotherapy interventions for pain and disability in people with CRPS I or II. We used a deliberately inclusive definition in an attempt to include evidence on any intervention that might reasonably be delivered within a physiotherapy context for people with CRPS. As a result, the included trials varied considerably but most were designed to test the specific effectiveness of individual modalities either alone, when added to other treatments or compared to other treatments. While these trials offered information about the specific or additional clinical benefits of those modalities, they are less informative about the effectiveness of physiotherapy programmes that incorporate multiple treatment modalities, but are more likely to reflect physiotherapy as it is delivered in clinical practice. Only one included trial took the pragmatic approach of testing a multimodal physiotherapy programme against a minimal treatment control group (Oerlemans 1999). Notably, this trial pre-dates substantial developments in the pathophysiological models of CRPS and it is possible that a modern multimodal physiotherapy programme might differ substantially. For example, we included 'pain education' within our search strategy but found no RCTs with pain neuroscience education (PNE) as the primary intervention. The 'pain exposure physical therapy' intervention in the trial by Barnhoorn 2015 appeared to contain some elements of the PNE approach and we know of one published case study where PNE was combined with GMI and graded functional exposure (Shepherd 2018). In addition, few of the included trials reported on adverse effects (five out of 34 trials) and it is unclear whether or not this represents an absence of adverse effects or a failure to report them. Only nine of the 34 included trials employed medium- to long-term follow-up of trial participants (Barnhoorn 2015; Cacchio 2009a; den Hollander 2016; Halicka 2021; Li 2012; Moseley 2005; Moseley 2006; Oerlemans 1999; Ryan 2017). The general lack of long-term follow-up of trial participants also limits the applicability of the evidence.

While we categorised these interventions under the label 'physiotherapy' in this Cochrane Review, we recognise that rehabilitation therapies may be delivered by a range of different professionals, including occupational therapists and nurses. Also, our main outcomes of interest were pain and disability. We did not assess outcomes related to emotional wellbeing, which we acknowledge are an important dimension of people's pain experience. Such outcomes were generally not measured in the included trials but could be included in future clinical trials and systematic reviews of interventions for CRPS.

Quality of the evidence

As reflected by the GRADE ratings, the overall certainty of the evidence in this Cochrane Review was very low. This reflects the fact that most included trials were at unclear or high risk of bias for criteria included under the standard domains of the Cochrane risk of bias tool, and under the additional risk of bias criteria of study size and duration included in this review. The included trials studied a broad range of interventions, which afforded us limited opportunity to pool data and that, coupled with study size, led to issues of imprecision and inconsistency. We were only able to combine trials through meta-analysis for one type of intervention (GMI) because of poor standards of reporting, insufficient data and clinical heterogeneity.

It is likely that small study effects, wherein there is a propensity for smaller published studies to report inflated effect sizes (Dechartres 2013; Moore 2012; Nüesch 2010), might lead to an overly positive picture for some interventions, particularly in a field with such a limited evidence base. A review of meta-analyses has demonstrated that trials with fewer than 50 participants, which reflects most trials (28/34) included in this Cochrane Review, returned effect estimates that were on average 48% larger than the largest trials and 23% larger than estimates from studies with sample sizes of more than 50 participants (Dechartres 2013). A recent Cochrane systematic review of psychological therapies for the management of chronic pain excluded studies with 19 or fewer participants in each trial arm because of the risk of bias associated with small sample sizes in RCTs (Williams 2020). This exclusion criterion has been recommended for systematic reviews of clinical trials involving patient populations with chronic pain (Busse 2015). Applying the same exclusion criterion would have resulted in the exclusion of over half of the trials (20/34) included in this review.

We did not downgrade any of the GRADE judgements on the basis of publication bias, as there can be no direct evidence with so few trials for any given intervention. Moreover, it is accepted that existing approaches to detecting publication bias are unsatisfactory. To an extent our GRADE judgements reflect this risk through the assessment of imprecision and the limitations of included trials. Conversely, the issue of small study size combined with low number of trials for any single comparison raises the possibility of false negatives through lack of statistical power (Button 2013). Many of the comparisons we included in this review did not demonstrate clear evidence of benefit of the index intervention.

The quality of reporting in many included trials was problematic. There was a lack of detailed descriptions of some interventions, which impedes judgements concerning the replicability and generalisability of some trials. To improve this, we recommend that trialists follow the Template for Intervention Description and Replication guidelines for better reporting of interventions (Hoffman 2014). In addition, a number of included trials did not present key numerical outcome data for all time points (19/34 trials) or insufficiently reported the scoring properties of their outcome measures for pain intensity (10/34 trials). The quality of reporting of pain-related outcome measures in clinical trials and observational studies is frequently insufficient (Smith 2015). In a systematic review assessing the quality of pain intensity reporting in three prominent pain journals, Smith 2015 found that nearly one-quarter of published studies inadequately reported the type of pain intensity measure employed. The choice of outcome measures for pain and function/disability varied across the trials included in this review, a finding consistent with a recent systematic review evaluating the use of outcome measures in clinical trials of pain management, rehabilitation and psychological interventions for CRPS (Grieve 2016b). Recommendations for a first core outcome measurement set in clinical trials for complex regional pain syndrome have recently been proposed (Grieve 2017) which, if adopted, would facilitate more valid comparisons between trials as well as the pooling of data for meta-analyses in order to obtain more precise estimates of treatment effect.

To our knowledge, only six of the 16 new trials included in this updated review were either registered or were associated with a published trial protocol (Barnhoorn 2015; den Hollander 2016; Halicka 2021; Lewis 2021; Ryan 2017; Strauss 2021). This fact, together with the poor standards of reporting that we observed in many of the unregistered studies included in this review, raises serious concerns regarding the validity of the majority of these unregistered trials, and their findings, as well as the potential for publication bias (Viergever 2014). This also shows that there are still academic journals willing to publish RCTs without prospective registration. We respectfully urge all trialists investigating physiotherapy interventions for CRPS to prospectively register their trial and publish a trial protocol in accordance with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines (Chan 2013). We also invite journal editors to give serious consideration to this issue before publishing unregistered trials (ICMJE 2019).

Potential biases in the review process

We conducted extensive and sensitive literature searches and included trials regardless of the language of publication. The choice to use the IMMPACT thresholds to determine the clinical importance of effect sizes is potentially controversial. What exactly constitutes an important difference on any given outcome measure remains contentious as the construct of a generic importance thresholds for a variety of interventions fails to reflect that patient satisfaction might differ substantially between interventions given their risks, costs and inconvenience, the point in the care pathway at which the participant arrives, and a range of other possible factors. Moreover, the IMMPACT thresholds are based on estimates of the degree of within-person change from baseline that participants might consider to be clinically important, whereas the effect sizes focused on in this review reflect the average change between intervention-groups following the interventions. It is possible that a small average between-group effect size might reflect that a proportion of participants responded very well to the intervention tested but equally it might reflect that most participants experienced a small effect. While we planned to include the results of 'responder analyses', which compare the proportion of participants achieving a clinically important improvement from baseline in the treatment and control groups, no studies reported these data.

Since the publication of our original protocol for this review (Smart 2013), the OMERACT 12 group reported recommendations for minimally important difference for pain outcomes (Busse 2015). The group recommends a threshold of 10 mm on a 0 to 100 visual analogue scale (VAS) as the threshold for minimal importance for average between-group change, though stress that this should be interpreted with caution as it remains possible that estimates that fall closely below this point may still reflect a treatment that benefits an appreciable number of participants. Using this largely more lenient threshold would not alter our conclusions regarding clinical importance. The OMERACT thresholds present similar problems to those associated with all generic thresholds and it seems likely that the discussion around what constitutes clinical importance will continue. Arguably, the thresholds used in this Cochrane Review of a 15% or 30% improvement in baseline levels of pain that are specifically attributable to the interventions do not represent unreasonably high thresholds.

Agreements and disagreements with other studies or reviews

The results of this updated systematic review remain largely consistent with the findings of a Cochrane overview of systematic reviews of all interventions for CRPS (O'Connell 2013), which drew its conclusions mainly based on two non-Cochrane reviews of physiotherapy interventions for CRPS (Daly 2009; Smith 2005). Daly 2009 concluded that there was good to very good-quality evidence to support the use of GMI for CRPS. Smith 2005 concluded that there was some evidence that exercise, acupuncture, TENS, relaxation techniques, mirror therapy, GMI and combined treatment programmes may be helpful and that it was not possible to determine the effectiveness of individual treatments for CRPS I. A subsequent systematic review of GMI for chronic pain (of which review author NOC was a co-author) concluded that there was limited evidence to suggest that GMI may be effective for CRPS (Bowering 2013). In O'Connell 2013, we concluded that there was low-quality evidence for the effectiveness of GMI. In this Cochrane Review we downgraded the GRADE rating for the certainty of evidence related to GMI to very low, largely due to the inconsistency introduced by the inclusion of Schreuders 2014. In Schreuders 2014, the trial authors adjusted the treatment schedule compared to the schedules delivered

by Moseley 2004 and Moseley 2006, though it was based on the same theoretical model. A more recent systematic review of treatments for CRPS identified a potential therapeutic role for mirror therapy, aerobic exercise and virtual body swapping (Duong 2018). Our analyses somewhat concur with those of Duong 2018 with respect to mirror therapy and aerobic exercise in that we found very low-certainty evidence in support of these interventions but larger, more robust trials of these interventions with longer follow-up are required in order to provide more accurate and clinically meaningful estimates of their treatment effect. We found low-certainty evidence from two small studies at high risk of bias that a single session of virtual body swapping does not improve pain in CRPS.

Recent clinical guidelines from the USA and the UK have placed rehabilitation therapies as first-line treatments for people with CRPS (Goebel 2018; Harden 2013). Both guidelines describe and recommend an extensive range of possible physiotherapy modalities that might be employed. In making their recommendations, these guidelines (unlike this Cochrane Review) draw on evidence from non-randomised studies, panel consensuses and expert opinion. This Cochrane Review highlights the fragility of the evidence underpinning these recommendations. The optimal approach to physiotherapy for people with CRPS and the true extent of potential benefits and risks remain uncertain. Also, there may be substantial redundancy within the broad range of therapies described or recommended in the guidelines.

AUTHORS' CONCLUSIONS

Implications for practice

For adults with complex regional pain syndrome (CRPS)

The evidence is very uncertain about the effects of any of the physiotherapy interventions identified in this review, including multimodal physiotherapy, exposure-based interventions and graded motor imagery, on the pain and disability of CRPS I at short-, medium- or long-term follow-up when compared to various active control interventions. Despite the uncertainty, it is likely that, in line with contemporary clinical guidelines, physiotherapy and rehabilitation-based interventions will continue to be recommended as first-line treatments for people with CRPS.

For clinicians

There is insufficient evidence to draw any conclusions regarding the effectiveness of any of the physiotherapy interventions for CRPS I identified in this review. Multimodal physiotherapy, aerobic exercise, graded motor imagery, mirror therapy, virtual reality, TENS and 'exposure in vivo' may reduce pain and/or disability for people with CRPS I when compared to various active control interventions but the evidence is very uncertain. These effects were mainly only apparent at short-term follow-up. However, we have very little confidence in the current evidence. In light of the uncertainty we encourage clinicians to remain up to date with the evidence and consider ways to present this information in meaningful ways to patients that enables them to make informed decisions regarding their care. In this knowledge vacuum clinicians' treatment selection is extremely challenging and is likely to be based on their training, access to relevant expertise and support and personal preferences. Well designed, executed and reported randomised controlled trials (RCTs) are critical to better guide future patient care. We are unable to draw any conclusions regarding physiotherapy interventions for CRPS II since we found only one small clinical trial for people with CRPS II exclusively.

For policy makers and funders of interventions

The results of this review highlight the uncertainty regarding the effectiveness of any physiotherapy interventions for CRPS I or II. Despite the substantial uncertainty, clinical guidelines recommend rehabilitation therapies as a core treatment for CRPS. The challenge lies in an inability to specifically recommend any one or combined therapeutic approach. Such recommendations remain entirely contingent on the availability of data from future well-designed and implemented clinical trials. We can say with certainty that the current state of the evidence supports the allocation of research funding for further clinical trials of physiotherapy for CRPS.

Implications for research

General implications

Overall, given the existing limitations within the current body of evidence, there is a clear need for further research into physiotherapy interventions in people with CRPS but many challenges remain in addressing this problem. Given the relatively low incidence of CRPS, it is likely to be difficult to recruit adequate numbers of participants to clinical trials. It seems likely that the best chance of addressing this challenge is through multicentre, collaborative research projects aimed at recruiting participants from potentially larger pools of clinical populations. The use of telehealth/telerehabilitation trials could facilitate this. It seems unlikely that it will be possible to generate sufficient evidence to support the many individual modalities currently applied to people with CRPS. In this instance there remains a case for taking a pragmatic approach to developing contemporary multi-modal, individually tailored 'best practice' models of physiotherapy care and prioritising trials of these programmes against usual or minimal care. Such trials might provide pragmatic estimates of effectiveness that best reflect the value of guideline recommended practice. Larger replication trials of graded motor imagery (GMI) and mirror therapy in particular would also be useful in order to provide more accurate estimates of treatment effect for these interventions, which current evidence suggests could offer meaningful clinical benefit.

Design implications

Large, high-quality randomised controlled trials, with cost-effectiveness analyses, are needed to investigate the effectiveness of physiotherapy interventions for CRPS. Where such sample sizes are not attainable, future RCTs should, at the very least, be prospectively registered and have a published trial protocol (in accordance with the SPIRIT guidelines; Chan 2013). Future trials should adhere to CONSORT guidance, including that related to the reporting of the development and evaluation of complex interventions (Möhler 2015). There should be a clear rationale outlining the mechanisms that underpin the intervention's effects and how the intervention might affect the outcomes of interest. Mechanism-specific rehabilitation strategies, whereby treatment selection is based on clinical assessment findings that are thought to reflect the underlying mechanisms of a given patient's CRPS, have been suggested (Packham 2018). Furthermore, trialists should use established diagnostic criteria, clearly report the type and aetiology of CRPS under investigation and adequately describe interventions (according to the TIDieR guidelines; Hoffman 2014). It

is our observation that rehabilitation-based interventions for CRPS often require the ongoing active participation of patients, in the clinic, at home or both. They also have the potential to worsen patients' pain. We invite trialists to accurately report reasons for dropouts from trial arms in an attempt to record and quantify the potential burdensomeness and/or unacceptability of interventions to patients. Accurately reporting reasons for dropout might help rank treatments of apparently equivalent efficacy (or with similarly lacking evidence of efficacy) in terms of what is practicable and least likely to harm. Recommendations for the design of clinical trials of pain interventions are available (Busse 2015; Dworkin 2008; Dworkin 2009; Dworkin 2010; Turk 2008a; Turk 2008b). Finally, when therapeutic exercise is the main or significant component of an intervention, trialists could consider self-assessing the therapeutic quality of the exercise programme included in their trial using the i-CONTENT tool, for example (Hoogeboom 2020).

Measurement implications

The wide variety of outcome measures used together with the poor quality of reporting of trial data in a number of studies included in our review highlights the need for trialists to use core outcome sets (Grieve 2016b), adequately report their scoring properties and interpretation, report point estimates with measures of variation for all outcomes at all time points and follow up participants over clinically meaningful lengths of time. Doing so would facilitate comparisons across studies and the statistical pooling of outcome data. A core set of standardised outcome measures for use in CRPS clinical research that might enhance consistency of use and standards of reporting has been developed (Grieve 2017). There is a pressing need to improve the measurement and reporting of adverse effects in this field. In the absence of any consensus or evidence regarding cut-points from which to interpret the magnitude of clinically important differences in pain intensity based on between-group differences at post-intervention time points (Dworkin 2009), trialists, clinicians, policymakers and funders may choose to follow IMMPACT or OMERACT guidance (Busse 2015; Dworkin 2008) until such time as further evidence to guide such decision-making becomes available.

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Editorial and peer-review contribution

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The following people conducted the editorial process for this article:

- Sign-off Editor (final editorial decision): Christopher Eccleston, Centre for Pain Research, The University of Bath, UK
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- Assistant Managing Editor (selected peer reviewers, collated peer-reviewer comments, conducted editorial checks and supported editorial team): Kerry Harding (Oxford University Hospitals (OUH) NHS Foundation Trust, Oxford, UK)
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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Askin 2014

Study characteristics	
Methods	**Design:** parallel-group, 3-arm, single-blind RCT **Setting:** outpatient hospital clinic (Turkey; dates not reported) **Interventions:** conventional care plus low-dose, high-frequency ultrasound therapy (0.5 watts/cm^2) for stellate ganglion blockade or conventional care plus low-dose, high-frequency ultrasound therapy (3.0 watts/cm^2) for stellate ganglion blockade or conventional care plus placebo ultrasound therapy **Sample size calculation:** not reported
Participants	**Number of participants:** 45 (15 in each group)

Askin 2014 *(Continued)*

Type of noxious initiating event: mixed (fracture of the distal radius (n = 17), tendon injury (n = 10), hand contusion (n = 5), postsurgery for carpal tunnel syndrome (n = 4), fracture of the elbow (n = 2), fracture of the humerus (n = 1), fracture of the finger (n = 1)) (upper limb)

Diagnostic criteria: Bruehl 1999 (CRPS I)

Baseline characteristics:

1. Conventional care plus low-dose, high-frequency ultrasound therapy (0.5 watts/cm^2) for stellate ganglion blockade:
   a. Mean (range) age = 45 (23 to 69) years; female:male = 7:6
   b. Mean (range) duration of CRPS I 57 (38 to 156) days
2. Conventional care plus low-dose, high-frequency ultrasound therapy (3.0 watts/cm^2) for stellate ganglion blockade:
   a. Mean (range) age = 46 (23 to 69) years; female:male = 7:6
   b. Mean (range) duration of CRPS I 62 (26 to 161) days
3. Conventional care plus placebo ultrasound therapy:
   a. Mean (range) age = 44 (22 to 69) years; female:male = 5:9
   b. Mean (range) duration of CRPS I 70.5 (15 to 162) days

Inclusion criteria:

1. Upper limb CRPS I

Exclusion criteria:

1. Peripheral or central nerve lesions
2. Diabetes mellitus
3. Severe heart failure
4. Severe hypertension
5. Cardiac conduct disorders
6. Chronic obstructive pulmonary disease
7. Chronic alcoholism
8. Rheumatologic disease
9. Malignancy
10. Thyroid disease
11. Participants using anticholinergic or antihypertensive medication

Interventions	Participants in all 3 groups received conventional care including: 1. pharmacotherapy (including 500 mg/day vitamin C, gabapentin (dose: 1800 mg/day) and prednisolone (dose: 30 mg/day - 2 weeks, stopped within next 2 weeks)); 2. 20 sessions of transcutaneous electrical nerve stimulation ((Enraf Nonius brand Endomed 582ID) 100 hertz (Hz) frequency to the painful area of the affected extremity once a day, 20 minutes); 3. contrast bath applications ((Ewac brand device) by immersing the affected upper extremity into hot (38°C) water for 4 minutes and then cold water (4°C) for 1 minute for a total 20 minutes); and 4. exercise (active, active assistive and passive range of motion exercises to the wrist and fingers, stretching exercises, progressive resistance exercises, performed as 2 sets of 15 repetitions for each exercise, once per day, plus mirror box exercises (details not reported) for 30 minutes). **Conventional care plus low-dose, high-frequency ultrasound therapy (0.5 watts/cm^2) (n = 15)** Components of intervention: using a Enraf Nonius Sonopuls (590 model) therapeutic ultrasound of the stellate ganglion was applied by placing the 1 cm^2 ultrasound head at the level of transverse process of the 7th vertebra and 3 cm to 4 cm above the sternoclavicular joint, using a 1 MHz frequency and pulsed pattern of 1:4 Dosage: 0.5 watts/cm^2, for 5 minutes

Askin 2014 *(Continued)*

	Frequency of administration: not reported (5 times per week for 4 weeks (20 sessions)) (Askin, personal communication). Provider: not reported **Conventional care plus low-dose, high-frequency ultrasound therapy (3.0 watts/cm^2) (n = 15)** Components of intervention: ultrasound procedure as described above Dosage: 3.0 watts/cm^2, for 5 minutes Frequency of administration: 5 times per week for 4 weeks (20 sessions) Provider: not reported **Conventional care plus placebo ultrasound therapy (n = 15)** Components of intervention: ultrasound procedure as described above, with the machine turned off
Outcomes	Time points at which outcomes were measured were not explicitly specified in the trial report. Outcomes were assessed at baseline and on completion of the intervention period (4 weeks post recruitment) (Askin, personal communication). The trial authors did not state any primary outcome. 1. Self-rated pain intensity at rest using a 10 cm VAS (0 = no pain, 10 = severe pain) 2. Limitation of total finger flexion was assessed by measuring finger pulp-distal crease distance using a ruler 3. Grip strength was assessed using a hand dynamometer (average of 3 measurements in kg) 4. Self-reported upper extremity disability was assessed using the Disability of the Arm, Shoulder and Hand (DASH) questionnaire (Turkish version), with higher scores indicating worse disability (score range not reported)
Notes	**Source of funding:** not reported **Statement regarding declarations of interest:** none declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "Patients were randomly divided into 3 groups by picking cards in different colours. First, three groups of cards (each group consisted of 15 cards) in 3 different colours (blue for 3 watts/cm2, pink for 0.5 watts/cm2, yellow for placebo) were prepared. Participants were asked to choose a card before starting the treatment. The US dose was determined according to the colour of the selected card and it was recorded. The randomisation process was performed by another physician". Comment: the trial authors used a non-random sequence generation process.
Allocation concealment (selection bias)	Unclear risk	Comment: the trial authors did not report the method of allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "No information was given to patients and to the physician who will make assessments and US application about the randomisation process until the end of the study". Comment: the participants were blinded to treatment allocation.
Blinding of outcome assessment (detection bias) Self-reported outcomes	Low risk	Quote: "No information was given to patients and to the physician who will make assessments and US application about the randomisation process until the end of the study".

Askin 2014 *(Continued)*

Blinding of outcome assessment (detection bias) Investigator-administered outcomes	Low risk	Quote: "No information was given to patients and to the physician who will make assessments and US application about the randomisation process until the end of the study".
Incomplete outcome data (attrition bias) Dropout rate described and acceptable	Low risk	Quote: "Thirteen patients from group I, 13 patients from group II and 14 patients from group III, a total of 40 patients completed the study". Comment: an overall dropout rate of 11% is unlikely to have biased the results.
Incomplete outcome data (attrition bias) Participants analysed in the group to which they were allocated	High risk	Quote: "Two patients from group I, 2 patients from group II and 1 patient from group III who did not come to therapy sessions regularly were excluded". Comment: the trial authors excluded 5 participants in violation of the ITT principle.
Selective reporting (reporting bias)	Low risk	Comment: outcome data were fully reported for all outcomes reported in the methods section of the publication.
Sample size	High risk	Quote: "Fourty-five patients with CRPS type I were randomly allocated into three groups". Comment: the small sample size may have introduced bias in the estimates of treatment effect.
Duration of follow-up	High risk	Quote: "Before and after the treatment the severity of the pain experienced at rest was assessed". Comment: outcomes were re-measured on completion of the intervention period only and were not measured over a clinically relevant length of time.
Other bias	Low risk	Comment: we did not identify any other sources of bias.

Aydemir 2006

Study characteristics	
Methods	**Design:** parallel-group, 3-arm, double-blind RCT **Setting:** Department of Physical Medicine and Rehabilitation Clinic, Gulhane Military Medical Academy (Turkey; dates not reported) **Interventions:** stellate ganglion block (SGB) with lidocaine and sham SGB with ultrasound (US) or SGB with US and sham SGB with lidocaine or sham SGB with lidocaine and sham SGB with US **Sample size calculation:** not reported
Participants	**Number of participants:** 25 (SGB with lidocaine (n = 9); SGB with US (n = 9); sham SGB with lidocaine and sham SGB with US (n = 7)) **Type of noxious initiating event:** mixed (trauma n = 12, fracture n = 11, idiopathic n = 2) (upper limb) **Diagnostic criteria:** Bruehl 1999 (CRPS I) **Baseline characteristics:** 1. SGB with lidocaine: a. Mean (±) age = 21.9 (1.05) years; female:male = not reported (assumed to be all males as setting identical to (Hazneci 2005)

Aydemir 2006 *(Continued)*

b. Mean (SD) duration of CRPS I = not reported

2. Group receiving SGB with US:
   a. Mean (±) age = 21.4 (0.73) years; female:male = not reported (assumed to be all males)
   b. Mean (SD) duration of CRPS I = not reported
3. Group receiving sham SGB with lidocaine and US:
   a. Mean (±) age = 21.1 (0.38) years; female:male = not reported (assumed to be all males)
   b. Mean (SD) duration of CRPS I = not reported

Inclusion criteria:

1. CRPS I

Exclusion criteria:

1. Peripheral or central nervous system lesion affecting the upper limb
2. Participants using anti-hypertensive or anti-cholinergic medications
3. Lidocaine allergy
4. Cardiac arrhthymias
5. History of stellate ganglion blockade within the last month

Interventions	Participants in all 3 groups received 21 sessions of exercise (active, active assisted, passive exercises for the wrist and fingers, twice daily supervised by the same physiotherapist), contrast baths (extremities were put in 38 °C hot water, 4 °C cold water for 4 minutes hot and 1 minute cold, 4 minutes cold and 1 minute hot and 4 minutes cold (total time 14 minutes)), transcutaneous electrical nerve stimulation (Enraf Nonius Endomed 582 instrument; for a period of 20 minutes with a frequency of 100 Hz), external pneumatic compression (involved extremity was compressed by a pressure of 50 mmHg for a period of 60 seconds and then pressure was released for 20 seconds and this compression and release procedure was repeated for 15 minutes, for participants who could not tolerate the 50 mmHg pressure a lower level pressure was used) and paracetamol (500 mg orally every 4 hours, maximum dosage of 3 g/daily was given if it is needed). **Stellate ganglion block with lidocaine (n = 9)** Components of intervention: 1. 10 mL of 1% lidocaine was injected slowly into the stellate ganglion (on the line of 6th vertebra, 1.5 cm lateral of the median line, 4 cm to 5 cm under the skin) 2. (Sham SGB with US) using a Enraf Nonius Sonopuls 590 and with the machine turned off the instrument was put on the ganglion for 5 minutes Dosage: 10 mL of 1% lidocaine Frequency of administration: not reported Provider: anaesthetist (other providers not reported) **Stellate ganglion block with ultrasound (n = 9)** Components of intervention: 1. (Sham SGB with lidocaine) 10 mL saline solution was used as placebo and injected slowly into the stellate ganglion 2. SGB with US was applied by using Enraf Nonius Sonopuls 590 (further details regarding method of application not reported) Dosage: 3 watt/cm^2 for 5 minutes Frequency of administration: not reported Provider: anaesthetist (other providers not reported) **Sham stellate ganglion block with lidocaine and ultrasound (n = 7)**

Aydemir 2006 *(Continued)*

	Components of intervention: 1. (Sham SGB with lidocaine) 10 mL saline solution was used as placebo and injected slowly into the stellate ganglion 2. (Sham SGB with US) using a Enraf Nonius Sonopuls 590 and with the machine turned off the instrument was put on the ganglion for 5 minutes Dosage: n/a Frequency of administration: not reported Provider: anaesthetist (other providers not reported)
Outcomes	Outcomes assessed at baseline, after treatment and 1 month post-treatment: 1. Self-reported spontaneous pain measured using a 10 cm VAS (0 to 10) (anchor points not reported) 2. Self-reported provocative pain measured using a Likert-type scale (0 = no pain, 1 = mild pain with deep palpation, 2 = serious pain with deep palpation, 3 = serious pain with superficial palpation, 4 = hyperaesthesia) (further details not reported) 3. Oedema measured using a standard forearm volumeter (measured in mL, further details not reported) 4. Finger pulp-distal palmer crease distance (measured in cm, further details not reported) 5. Grip strength measured using a Jamar dynamometer, in a sitting position (measured in kg) 6. Functional hand scale (score range 0 to 19 with higher scores indicating worse disability) 7. Keitel index score (score range 4 to 42; interpretation of scores not reported)
Notes	**Source of funding:** not reported **Statement regarding declarations of interest:** not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomised by envelope method and 3 groups were established". Comment: "Treatment orders were made online..." Comment: it is likely that the trial authors used an acceptable method to generate the allocation sequence.
Allocation concealment (selection bias)	Unclear risk	Quote: "Patients were randomised by envelope method and 3 groups were established". Comment: the trial authors did not adequately report the method of allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The study was designed as a double blind study. Treatment orders were made online and except the personnel who were involved in the therapy nobody even the doctor was aware of the selected method". Comment: participants were likely to have been adequately blinded.
Blinding of outcome assessment (detection bias) Self-reported outcomes	Low risk	Quote: "The study was designed as a double blind study. Treatment orders were made online and except the personnel who were involved in the therapy nobody even the doctor was aware of the selected method". Comment: participants who completed self-reported outcome measures were blinded to treatment allocation.

Aydemir 2006 *(Continued)*

Blinding of outcome assessment (detection bias) Investigator-administered outcomes	Low risk	Quote: "Treatment orders were made online and except the personnel who were involved in the therapy nobody even the doctor was aware of the selected method". Comment: the outcome assessor was blinded to the treatment allocation.
Incomplete outcome data (attrition bias) Dropout rate described and acceptable	Unclear risk	Comment: the dropout rate was not reported.
Incomplete outcome data (attrition bias) Participants analysed in the group to which they were allocated	Unclear risk	Comment: the method of analysis (ITT versus per protocol) was not reported.
Selective reporting (reporting bias)	Low risk	Comment: the trial authors fully reported outcome data for all outcomes reported in the methods section of the publication.
Sample size	High risk	Quote: "Twenty-five patients were divided into three groups". Comment: the small sample size may have introduced bias in the estimates of treatment effect.
Duration of follow-up	Unclear risk	Quote: "These evaluations were performed before and after treatment and one month later". Comment: the clinical relevance of a 1-month follow-up of outcomes is uncertain.
Other bias	Low risk	Comment: we did not identify any other sources of bias.

Barnhoorn 2015

Study characteristics	
Methods	**Design:** parallel-group, 2-arm, single-blind RCT **Setting:** university hospital (Level 1 trauma centre) in a rural area of The Netherlands (The Netherlands; from 9 January 2009 to 7 March 2012) **Interventions:** pain exposure physical therapy (PEPT) or conventional treatment **Sample size calculation:** 62 patients (31 per group) were required based on an α of 0.05 and a power of 80% for a one-sided Chi^2 test, and based on an expected proportion of responders of 80% in the experimental group and 50% in the control group
Participants	**Number of participants:** 56 (28 in each group) **Type of noxious initiating event:** not reported (upper and lower limb) **Diagnostic criteria:** Harden 2007 (CRPS I) **Baseline characteristics:** 1. PEPT: a. Mean (SD) age = 43.7 (14.8) years; female:male = 24:4

Barnhoorn 2015 *(Continued)*

b. Upper limb 18
c. Mean (SD) time since event 7.0 (3.8) months

2. Conventional treatment:
   a. Mean (SD) age = 44.9 (18.5) years; female:male = 21:7
   b. Upper limb 19
   c. Mean (SD) time since event 7.5 (4.5) months

Inclusion criteria:

1. Confirmed diagnosis according to the Harden 2007 criteria
2. The first assessment took place between 3 and 24 months after the inciting event
3. Patients were between 18 and 80 years of age

Exclusion criteria:

1. Other causes for the signs and symptoms (e.g. non-union, osteomyelitis and CPRS II)
2. CRPS I in more than one extremity
3. Relapse of CRPS I
4. Pregnancy
5. Lactation
6. Prior sympathectomy of the affected extremity

Interventions	**PEPT (n = 28)** A functional form of physical therapy combined with a cognitive behavioural form of treatment. Components of intervention: 1. Progressive-loading exercises, tailored and focused on specific body functions using standard techniques in regular physical therapy, including passive and active exercises to mobilise joints and muscle stretching. During progressive loading, the physical therapists act mainly as instructors, rewarding functional progression and providing schedules for exercises and activities at home. 2. Desensitisation, using self-massage and forced use of the affected arm or leg in daily activities. 3. Information and education about CRPS I, PEPT and the role of chronic pain as a false warning sign. Dosage: 40 minutes per session Frequency of administration: maximum of 5 treatment sessions, with varying intervals between the sessions depending on the progression and personal needs of the patient Provider: physical therapists **Conventional treatment (n = 28)** Components of intervention: 1. Pharmacological treatment consisting of analgesics in a step-up procedure in accordance with the WHO's pain ladder 2. Physical therapy (TENS, walking aids, progressive-loading exercises, muscle strength training, joint mobility exercises) 3. Occupational therapy (splints) Dosage: not reported Frequency of administration: no predefined limits, on average 15 to 20 sessions Provider: anaesthesiologist, physical therapist, rehabilitation physician
Outcomes	Outcomes assessed at baseline and at 3, 6 and 9 months post randomisation

Barnhoorn 2015 *(Continued)*

1. Impairment level Sum Score - Restricted Version (ISS-RV) (primary outcome measure). ISS-RV contains four measurement instruments: visual analogue scale for pain (VAS-pain 1 to 10). (We note the unusual use of a VAS pain scale from 1 to 10 instead of 0 to 10), McGill Pain Questionnaire Dutch Language Version (MPQ-DLV), Active Range of Motion (AROM) of joints and skin temperature. Each element of ISS-RV is converted to a 1- to 10-point scale, which results in a sum score ranging from 4 to 40 points, higher values indicate more severe impairment).
2. Pain Disability Index (PDI) (score range 0 to 70, higher scores indicate worse disability)
3. Muscle strength (measured by a handheld dynamometer (MicroFET), reported as %=left-right difference, relative to the non-affected side)
4. Short Form 36 (SF-36) Questionnaire (score range 0 to 100, lower scores indicate worse health-related quality of life)
5. Disability of the arm, shoulder and hand, DLV (DASH-DLV) questionnaire (score range 0 to 100, higher scores indicate worse disability)
6. Lower Limb Tasks Questionnaire (LLTQ) (score range 0 to 40, lower scores indicate worse disability).
7. 10-metre walk test (10MWT) (in seconds)
8. Timed up-and-go test (TUG) (in seconds)
9. EuroQol-5D (EQ-5D) index (maximum score of 1)
10. EuroQol-5D (EQ-5D) VAS (score range 0 to 100, lower scores indicate worse health-related quality of life)

Notes	**Source of funding:** The Netherlands Organisation for Health Research and Development sponsored this study (grant number 170991004). The sponsor had no role in the study design, data collection, data analysis, data interpretation or writing of the report. **Statement regarding declarations of interest:** the authors declared no conflicts of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A statistician who had no clinical involvement in the trial designed a computerised randomisation program". Comment: the trial authors used an acceptable method to generate the allocation sequence.
Allocation concealment (selection bias)	Low risk	Quote: "An independent person allocated patients to one of the two treatment groups...in a 1:1 ratio using the randomisation program". Comment: the trial authors probably used an acceptable method to conceal the allocation sequence.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Given the nature of the interventions, it was not possible to blind the patients and the therapists". Comment: given the nature of the intervention, participants were not blinded to treatment and may have had different expectations about the benefits of each intervention.
Blinding of outcome assessment (detection bias) Self-reported outcomes	High risk	Comment: unblinded participants, who may have had different expectations about the benefits of the intervention they received, self-reported some outcomes (e.g. VAS for pain).
Blinding of outcome assessment (detection bias) Investigator-administered outcomes	Low risk	Quote: "The trained research nurse (TT) who performed all assessments prior to randomisation and during follow-up was blinded to the treatment allocation".

Barnhoorn 2015 *(Continued)*

		Comment: the outcome assessor of investigator-administered outcomes was blinded to treatment allocation.
Incomplete outcome data (attrition bias) Dropout rate described and acceptable	Low risk	Quote: "One patient in the PEPT group dropped out after two treatment sessions because of complete recovery. One patient in the CONV group was not confident about the treatment and was lost to follow-up. Another patient in the CONV group stopped without offering a reason". Comment: a small dropout rate is unlikely to have biased the results.
Incomplete outcome data (attrition bias) Participants analysed in the group to which they were allocated	Low risk	Quote: "We conducted the statistical analysis following the intention-to-treat principle (ITT): patients were analysed in the groups to which they were allocated". Comment: the trial authors analysed participants in the group to which they were allocated.
Selective reporting (reporting bias)	Unclear risk	Comment: the primary outcome measure was reported in accordance with the published protocol but there are a number of discrepancies in reported outcome measures between the published protocol and the trial report.
Sample size	High risk	Quote: "The resulting 56 patients were randomly allocated to either PEPT (n=28) or [conventional treatment] (n=28)" Comment: the small sample size may have introduced bias in the estimates of treatment effect.
Duration of follow-up	Low risk	Quote: "Further measurements are taken during the course of the treatment at three months (T1) and at the end of the treatment at six months (T2). Follow up is at nine months (T3) after inclusion". Comment: the trial authors measured outcomes over a clinically relevant length of time.
Other bias	Unclear risk	Quote: "This trial was prospectively registered at http://www.clinicaltrials.gov, NCT0081 7128". Quote: "The study protocol and rationale of both treatment strategies have been published elsewhere". Comment: the trial was prospectively registered and a trial protocol published. Quote: "Prior to treatment initiation, four patients (14%) in the PEPT group and 11 patients (39%) in the [conventional treatment] group opted out of their assigned treatment and switched groups". Quote: "During the course of the trial, three additional patients switched from [conventional treatment] to PEPT due to insufficient results with their treatment". Comment: a total of 14 (50% of the conventional treatment group) patients voluntarily switched groups, which may have compromised the internal validity of the study.

Benedetti 2018

Study characteristics

Benedetti 2018 *(Continued)*

Methods	**Design:** parallel-group, 2-arm, double-blind pilot RCT **Setting:** level-2 public outpatient clinic for orthopaedic rehabilitation (Italy; patients attending between 2013 to 2016 were considered eligible; exact trial dates not reported) **Interventions:** rehabilitation plus Bio-Electro-Magnetic-Energy-Regulation (BEMER) or rehabilitation plus placebo BEMER **Sample size calculation:** "Sample size (15 patients per group) was established a priori, based on a standard deviation of 1, a minimal clinically significant difference of 3 cm in the VAS between pre- and post-treatment, a significance of 0.05, and a power of > 0.8 using G*Power 3.1.9.2."
Participants	**Number of participants:** 30 (15 in each group) **Type of noxious initiating event:** mixed (post fracture n = 23, soft-tissue injury/condition n = 2, post surgery n = 4, postraumatic talar bone oedema n = 1 (upper or lower limb) **Diagnostic criteria:** "Budapest criteria" (Harden 2007) (CRPS I) **Baseline characteristics:** 1. Rehabilitation plus BEMER: a. Mean (SD) age = 56.6 (10.4) years; female:male = 14:1 b. Mean (SD) duration of CRPS I 94.9 (78.5) days 2. Rehabilitation plus placebo BEMER: a. Mean (SD) age = 56.8 (14.1) years; female:male = 13:2 b. Mean (SD) duration of CRPS I 83.2 (63.1) days **Inclusion criteria:** 1. Confirmed diagnosis of CRPS I (upper or lower limb) **Exclusion criteria:** 1. Patients with pacemakers 2. Metal prosthesis 3. Pregnant 4. Patients with primary or secondary confirmed neoplastic lesions
Interventions	Participants in both groups received rehabilitation for 2 hours per day, for 10 consecutive days, delivered by a physiotherapist, including: 1. information on the pathology (details not reported); 2. psychological support in the case of depression or anxiety symptoms; 3. motor rehabilitation (passive mobilisation, active assisted mobilisation, active mobilisation, desensitisation techniques, proprioceptive feedback, gait rehabilitation for patients with CRPS I of the lower limb, or perceptive motor therapy and occupational therapy for patients with CRPS I of the upper limb); 4. lymphatic massages; 5. 20 tramadol oral drops before physiotherapy was administered when needed (pain VAS > 6/10). **Rehabilitation plus BEMER (n = 15)** Components of intervention: Make and model of the device used to deliver BEMER not reported. Patients were treated with "total body" stimulation supplied by a flexible panel (180 × 50 cm) placed underneath the patient laying in supine position, and a local stimulation supplied by a flexible pad (50 × 15cm) positioned depending on the anatomical distribution of CRPS-I. The BEMER signal is made up of a sequence of PEMF induced by flat and flexible electric coils, with low frequency (< 33.3 Hz) and very low intensity (total body: 7 to 35 microTesla, local pad: 60 to 100 microTesla). The signal starts from lower values of intensity and increases by few microTesla at each pulse. In this way, the initial value of each pulse is higher than the previous one and the deviation from zero increases gradually up to the

Benedetti 2018 *(Continued)*

	maximal values. After that, the value decreases every 30 ms until it goes back to zero. After 2 minutes, the magnetic field changes its polarity. Dosage: 20 minutes per session Frequency of administration: once per day for 10 days Provider: physiatrists, physiotherapists **Rehabilitation plus placebo BEMER (n = 15)** Components of intervention: participants were positioned in the same way, the device was turned on but the treatment was not delivered Dosage: 20 minutes per session Frequency of administration: once per day for 10 days Provider: physiatrists, physiotherapists
Outcomes	Outcomes assessed at baseline, at the end of the 10-day treatment period and 1 month post-treatment 1. Self-reported pain measured using a 10 cm VAS (0 = no pain, 10 = worst imaginable pain) (primary endpoint) 2. Upper limb function assessed by Hand Grip Strength (HGS) in mm Hg by a sphygmomanometer 3. Upper limb motor disability measured using the Disabilities of the Arm, Shoulder, and Hand (DASH) score, with scores ranging from 0 (no disability) to 100 (most severe disability) 4. Lower limb disability measured using the Maryland Foot Score (MFS), with scores ranging from 0 to 100 (score interpretation not reported)
Notes	**Source of funding:** not reported **Statement regarding declarations of interest:** the authors declared no conflicts of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Simple randomization was formulated a priori using a system of computer-generated random numbers". Comment: the trial authors used an acceptable method to generate the allocation sequence.
Allocation concealment (selection bias)	Unclear risk	Quote: "According to the sequence of numbers obtained, patients were allocated in two groups". Comment: the trial authors did not adequately report the method of allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Since BEMER therapy does not give patients any sensation (e.g., feeling of warmth or tingling), patients were not aware of the difference and they were unaware of the group they belonged". Comment: the participants were blinded to treatment allocation. Comment: the trial authors did not report the procedure for blinding of care providers.
Blinding of outcome assessment (detection bias) Self-reported outcomes	Low risk	Quote: "Since BEMER therapy does not give patients any sensation (e.g., feeling of warmth or tingling), patients were not aware of the difference and they were unaware of the group they belonged".

Benedetti 2018 *(Continued)*

		Comment: the participants who completed self-reported outcome measures were blinded to treatment allocation.
Blinding of outcome assessment (detection bias) Investigator-administered outcomes	Low risk	Quote: "Assessment data were collected by a physiotherapist, and then analyzed by the statistician, blinded to the groups' assignment. Comment: the outcome assessor was blinded to treatment allocation.
Incomplete outcome data (attrition bias) Dropout rate described and acceptable	Low risk	Quote: "Thirty patients accepted to participate to the study and completed the follow-up assessment, 15 in each group". Comment: all randomly assigned participants completed the study.
Incomplete outcome data (attrition bias) Participants analysed in the group to which they were allocated	Unclear risk	Comment: the trial authors did not report the method of analysis (ITT versus per protocol).
Selective reporting (reporting bias)	Low risk	Comment: the trial authors fully reported outcome data for all outcomes reported in the methods section of the publication.
Sample size	High risk	Quote: "Thirty patients accepted to participate to the study and completed the follow-up assessment". Comment: the small sample size may have introduced bias in the estimates of treatment effect.
Duration of follow-up	Unclear risk	Quote: "Study participants were assessed at the beginning of treatment (T0), at the end of treatment (T1), and at follow-up (T2, 1 month after T1)". Comment: the trial authors did not measure outcomes over a clinically relevant length of time.
Other bias	Low risk	Comment: we did not identify any other sources of bias.

Bilgili 2016

Study characteristics	
Methods	**Design:** parallel-group, 2-arm RCT **Setting:** Physical Therapy and Rehabilitation Outpatient Clinic of Antalya Education and Research State Hospital (Turkey; recruitment from 2012 to 2013) **Interventions:** transcutaneous electrical nerve stimulation (TENS) plus standard physical therapy or sham TENS plus standard physical therapy **Sample size calculation:** not reported
Participants	**Number of participants:** 30 (15 in each group) **Type of noxious initiating event:** mixed (fracture of the distal radius (n = 21), excision of cystic mass from soft tissue (n= 2), fracture of the radial corpus (n = 1), fracture of the 1st metacarpal bone (n = 1), fracture of the radial head (n = 1), fracture of the scaphoid (n = 1), fracture of the olecranon and triceps tendon rupture (n = 1), ligament injury in the 5th proximal interphalangeal joint (n = 1), (1 case unaccounted for)) (upper limb) **Diagnostic criteria:** Merskey 1994 (Stage I or Stage II CRPS I)

Bilgili 2016 *(Continued)*

Baseline characteristics:

1. TENS:
   a. Mean (SD) age = 49.07 (10.26) years; female:male = 9:6
   b. Stage I (N, %) 11 (73.3%), Stage II 4 (26.7%)
   c. Mean (SD) duration of CRPS I = not reported
2. Sham TENS:
   a. Mean (SD) age = 45.20 (17.65) years; female:male = 7:8
   b. Stage I (N, %) 10 (66.7%), Stage II 5 (33.3%)
   c. Mean (SD) duration of CRPS I = not reported

Inclusion criteria:

1. Confirmed diagnosis of Stage I or II CRPS I

Exclusion criteria:

1. Presence of peripheral nerve injury
2. Presence of comorbid disease that could cause neuropathic pain such as diabetic neuropathy
3. Presence of renal dysfunction
4. Presence of a chronic pain syndrome (e.g. fibromyalgia, phantom pain, rheumatoid arthritis)
5. Conditions that cause disruption of skin and extremity integrity such as burns, large tissue defects or amputations
6. Intellectual disability
7. Unwillingness for participation
8. Any previous treatment for CRPS

Interventions	Participants in both groups received standard physical therapy, including contrast bath for 20 minutes; whirlpool bath for 15 minutes; assisted active and passive range of motion, and static stretching exercises up to the pain threshold (15 sessions). Participants were allowed to use paracetamol according to their pain status (maximum dose 4g/day). **TENS (n = 15)** Components of intervention: TENS was applied using a CHATTANOGA Intelect Mobile Stim 2777. Two carbon electrodes (6 × 8 cm in size) were placed on the involved extremity using wet pads, with the active electrode on the dorsal aspect of the forearm and the passive electrode on the dorsal aspect of the hand. Dosage: frequency 100 Hz, pulse duration, 50 ms to 100 ms; and amplitude that did not cause discomfort to the patient or muscle contraction Frequency of administration: not reported (total of 15 sessions) Provider: not reported **Sham TENS (n = 15)** Components of intervention: the electrodes were placed on the involved extremity in a similar manner. The TENS device was operated but no current was given. Frequency of administration: not reported (total of 15 sessions) Provider: not reported
Outcomes	Outcomes assessed at baseline and on completion of the intervention period. 1. Self-reported resting pain measured using a 10 cm VAS (0 = no pain to 10 = intractable pain) 2. Self-reported neuropathic pain measured using the Turkish version of the Leeds Assessment of Neuropathic Signs and Symptoms (LANSS) scale (scoring properties not adequately reported)

Bilgili 2016 *(Continued)*

3. Self-reported neuropathic pain measured using the Turkish version of the Douleur Neuropathique en 4 Questions (DN-4) with scores of ≥ 4/10 of greater indicating neuropathic pain
4. Upper limb oedema using volumetric measurements of water displacement (in millilitres)
5. Finger mobility, by measuring the distance between the 2nd to 5th finger pulp and distal palmar line, in centimetres using a ruler
6. Wrist mobility, assessed by measuring active wrist flexion, extension, radial and ulnar deviation using the neutral zero method with a standard goniometer
7. Hand grip strength was assessed using a hand dynamometer (average of 3 measurements in kg)
8. Self-reported functional disability was measured using the Duruöz Hand Index (DHI) (scoring properties not fully reported)

Notes	**Source of funding:** not reported **Statement regarding declarations of interest:** the authors declared no conflicts of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "Randomization was performed by a physician who did not participate in the study. Thirty cards with two distinct colors were prepared. The patients were asked to choose a card, which was then used to allocate the patient to one of the treatment groups." Comment: the trial authors used a non-random sequence generation process.
Allocation concealment (selection bias)	Unclear risk	Quote: "Thirty cards with two distinct colors were prepared. The patients were asked to choose a card, which was then used to allocate the patient to one of the treatment groups. The patients and physicians were blinded to the randomization". Comment: the trial authors did not adequately report the method of allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Sham TENS: The electrodes were placed on the involved extremity in a similar manner. The TENS device was operated but no current was given". Comment: given the nature of the intervention and our knowledge of TENS, we judge that the sham intervention did not control for the auditory and/or sensory characteristics of the real intervention and as such participants were not blinded to treatment and may have had different expectations about the benefits of each intervention.
Blinding of outcome assessment (detection bias) Self-reported outcomes	High risk	Comment: unblinded participants, who may have had different expectations about the benefits of the intervention they received, self-reported some outcomes (e.g. VAS for pain).
Blinding of outcome assessment (detection bias) Investigator-administered outcomes	Unclear risk	Quote: "The patients and physicians were blinded to the randomization". Comment: the trial authors did not provide a statement of procedures regarding blinding of the outcome assessor.
Incomplete outcome data (attrition bias) Dropout rate described and acceptable	Unclear risk	Comment: the trial authors did not report the dropout rate.
Incomplete outcome data (attrition bias)	Unclear risk	Comment: the trial authors did not report the method of analysis (ITT versus per protocol).

Bilgili 2016 *(Continued)*

Participants analysed in the group to which they were allocated		
Selective reporting (reporting bias)	Low risk	Comment: the trial authors fully reported outcome data for all outcomes reported in the methods section of the publication.
Sample size	High risk	Quote: "The study included 30 patients with stage 1 and 2 CRPS Type I in the upper extremities". Comment: the small sample size may have introduced bias in the estimates of treatment effect.
Duration of follow-up	High risk	Quote: "Only short-term follow-up results were evaluated with assessments performed at baseline and after treatment. No long-term results were available". Comment: the trial authors did not measure outcomes over a clinically relevant length of time.
Other bias	Low risk	Comment: we did not identify any other sources of bias.

Büyükturan 2018

Study characteristics	
Methods	**Design:** parallel-group, 2-arm, single-blind RCT **Setting:** Ahi Evran University Training and Research Hospital (Turkey; from September 2014 to February 2016) **Interventions:** electromagnetic field therapy (EMFT) plus physiotherapy or placebo EMFT plus physiotherapy **Sample size calculation:** assuming a large effect size, with a statistical significance level of 5% (P = 0.05), statistical power of 80%, and an effect size of 0.8, a minimum of 21 participants were required per group
Participants	**Number of participants:** 42 (21 in each group) **Type of noxious initiating event:** mixed (fractured elbow (n = 11), fractured distal radius (n = 10), fractured ulnar styloid process (n = 3), tendon injury (n = 9), hand contusion (n = 5), fractured shaft of humerus (n = 3, fractured index finger (n = 1)) (upper limb) **Diagnostic criteria:** Harden 2007 (CRPS I) **Baseline characteristics:** 1. EMFT: a. Mean age (SD) = 36.2 (8.54) years; female:male = 12:9 b. Duration of disease = 5.71 (± 1.45) weeks 2. Placebo EMFT: a. Mean age (SD) = 34.4 (7.45) years; female:male = 11:10 b. Duration of disease = 5.14 (± 1.89) weeks **Inclusion criteria:** 1. Diagnosed with CRPS I secondary to upper extremity trauma 2. Volunteering to participate in the study

Büyükturan 2018 *(Continued)*

	3. Being in the acute phase (not defined) of CRPS I **Exclusion criteria:** 1. Pregnant or in menopausal state 2. Malignant or infectious disease 3. Pacemaker 4. Previously received treatment related to CRPS I 5. Under 18 or over 64 years of age 6. Had contraindications for physical agents 7. Neurological abnormalities not related to CRPS I
Interventions	Participants in both groups were i) permitted to take non-steroidal anti-inflammatory drugs and/or analgesics and ii) received physiotherapy including passive (weeks 1 and 2), active-assistive (weeks 3 and 4), and active (weeks 5 and 6) daily range of motion (ROM) exercises for the wrist (flexion, extension, radial and ulnar deviation) and fingers (flexion and extension) (3 sets of 10 repetitions, 5 times per week for 6 weeks; total 30 sessions). Participants were also given 'instructions' and 'informative explanations' (details not reported). **EMFT (n = 21)** Components of intervention: treatment was administered using a MG WAVE Magnetotherapy (Via Canapa, Italy) device. Participants were positioned in supine lying with their affected extremity placed within a “sliding coil” electrode. Dosage: 100 Gauss intensity and 50 Hz frequency for 60 minutes Frequency of administration: once a day, 5 times a week, for 6 weeks (total of 30 sessions) Provider: physiotherapist **Placebo EMFT (n = 21)** Components of intervention: participants affected extremities were placed in the same device without it being switched on
Outcomes	Outcomes assessed at baseline and on completion of the intervention period 1. Self-reported pain (average pain felt in past week) measured using a 10 cm VAS (0 = none to 10 = extreme) 2. Self-reported kinesiophobia was evaluated using the Turkish version of Tampa Scale of Kinesiophobia (TSK) (score range 17 to 68; higher scores indicate greater perceived kinesiophobia) 3. Self-reported upper limb function was evaluated using the Quick-Disabilities of the Arm, Shoulder and Hand (Q-DASH) Scale (score range 0 to 100; higher scores indicate greater disability) 4. Wrist range of motion was evaluated using a hand goniometer (in degrees) 5. Third finger range of motion was evaluated using a ruler to measure the fingertip-to-distal palmar crease distance (in cm) 6. Hand oedema was measured using a figure of 8 method (method fully reported) (in cm) 7. Grip strength was measured using a Jamar Dynamometer (Lafayette Instrument, Model 7498-05, USA). The average of 3 measurements was calculated (in kg).
Notes	**Source of funding:** no funding was provided **Statement regarding declarations of interest:** none declared

Risk of bias

Bias	Authors' judgement	Support for judgement

Büyükturan 2018 *(Continued)*

Random sequence generation (selection bias)	High risk	Quote: "This study was a randomized, singleblinded and placebo-controlled trial". Quote: "Randomization was carried out using the sealed envelope system. Each participant picked up one of the 46 prepared envelopes that contained a card in a specific color". Comment: the trial authors used a non-random sequence generation process.
Allocation concealment (selection bias)	Unclear risk	Quote: "Randomization was carried out using the sealed envelope system. Each participant picked up one of the 46 prepared envelopes that contained a card in a specific color. They were placed in either EMFT or p-EMFT group depending on the color of the card inside their envelope". Comment: the trial authors did not adequately report the method of allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "So, everything was the same as the EMFT application, except for the fact that the device did not supply current". Comment: participants were likely to have been adequately blinded but the trial authors did not explicitly report the extent to which the placebo intervention controls for the auditory and sensory characteristics of the intervention. Comment: the trial authors did not adequately report the procedure for blinding of care providers.
Blinding of outcome assessment (detection bias) Self-reported outcomes	Low risk	Quote: "In p-EMFT application; the very same position of the patients and electrodes were used. However, the device was switched off. So, everything was the same as the EMFT application, except for the fact that the device did not supply current". Comment: the participants who completed self-reported outcome measures were probably blinded to treatment allocation.
Blinding of outcome assessment (detection bias) Investigator-administered outcomes	Unclear risk	Quote: "Assessments and evaluations, however, were done both at baseline and at the end of the training by same researcher". Comment: the trial authors did not provide a statement of procedures regarding blinding of the outcome assessor.
Incomplete outcome data (attrition bias) Dropout rate described and acceptable	Low risk	Quote: "All patients successfully completed the whole treatment program". Comment: all randomly assigned participants appear to have completed the study.
Incomplete outcome data (attrition bias) Participants analysed in the group to which they were allocated	Unclear risk	Comment: the trial authors did not report the method of analysis (ITT versus per protocol).
Selective reporting (reporting bias)	Low risk	Comment: the trial authors fully reported outcome data for all outcomes reported in the methods section of the publication.
Sample size	High risk	Quote: "Forty-two individuals were randomly assigned into either EMFT (N=21) or placebo EMFT (p-EMFT) (N=21) groups". Comment: the small sample size may have introduced bias in the estimates of treatment effect.

Büyükturan 2018 *(Continued)*

Duration of follow-up	High risk	Quote: "Assessments and evaluations, however, were done both at baseline and at the end of the training by same researcher". Comment: the trial authors did not measure outcomes over a clinically relevant length of time.
Other bias	Low risk	Comment: we did not identify any other sources of bias.

Cacchio 2009a

Study characteristics	
Methods	**Design:** parallel-group, 2-arm, single-blind RCT **Setting:** inpatient and outpatient rehabilitation centre (Italy; October 2000 to December 2006) **Interventions:** mirror therapy or placebo control (covered mirror) **Sample size calculation:** 24 participants per group required to detect a 2 cm reduction in pain on a 10 cm VAS (SD 1.5) with 0 cm labelled as "no pain" and 10 cm as "worst pain I have ever had" at 1 week after treatment at 1% level of statistical significance with 90% power, including a 30% rate of loss at follow-up
Participants	**Number of participants:** 48 (24 per group) **Type of noxious initiating event:** stroke (upper limb) **Diagnostic criteria:**Bruehl 1999 (CRPS I) **Baseline characteristics:** 1. Conventional stroke rehabilitation plus mirror therapy: a. Mean (SD) age = 57.9 (9.9) years; female:male = 13:11 b. Mean (SD) duration of CRPS I 2.8 (1.3) months 2. Conventional stroke rehabilitation plus placebo control: a. Mean (SD) age = 58.8 (9.4) years; female:male = 13:11 b. Mean (SD) duration of CRPS I 2.6 (1.5) months **Inclusion criteria:** 1. First episode of unilateral stroke with hemiparesis during the previous 6 months 2. VAS (0 to 10 cm) pain score > 4 cm **Exclusion criteria:** 1. Ipsilateral intra-articular shoulder injection within the last 6 months or use of systemic corticosteroids with the previous 4 months 2. Presence of another obvious explanation for the pain 3. Prior surgery to either shoulder or neck region 4. Serious uncontrolled medical conditions 5. Global aphasia, cognitive or visual impairments interfering with testing or treatment 6. Visual impairment that might interfere with the trial aims 7. Evidence of recent drug or alcohol abuse or severe depression
Interventions	Participants in both groups received 4 weeks of conventional stroke rehabilitation comprising neuro-rehabilitation techniques, occupational therapy (OT) and speech therapy (if required), consisting of 5 x 1-hour sessions per week.

Cacchio 2009a *(Continued)*

	Conventional stroke rehabilitation plus mirror therapy (n = 24) Components of intervention: mirror therapy programme: whilst seated with a mirror board positioned between the upper limbs, perpendicular to the midline and with the unaffected limb facing the reflective surface and with their affected upper limb hidden from view, participants observed the reflection of their unaffected upper limb while performing flexion and extension at the shoulder, elbow and wrist and pronation and supination of the forearm. Dosage: 30 minutes per session (for the first 2 weeks), 1 hour per session (for the second 2 weeks) Frequency of administration: 5 times per week for 4 weeks (20 sessions) Provider: physiotherapist **Conventional stroke rehabilitation plus placebo control (n = 24)** Components of intervention: participants performed the same exercises, according to the same dosage and frequency, with the reflective mirror surface covered
Outcomes	Outcomes assessed at baseline and at 1 week and 6 months post-treatment **Primary outcomes:** 1. Self-rated pain intensity at rest using a 10 cm horizontal VAS labelled "no pain" to "worst pain I have ever had" (pain location not reported) 2. Self-rated pain intensity on shoulder movement (forward flexion) using a 10 cm VAS labelled "no pain" to "worst pain I have ever had" 3. Brush evoked tactile allodynia, assessed by means of 3 brush movements within the area of maximum pain, using a 10 cm VAS labelled "no pain" to "worst pain I have ever had" **Secondary outcomes:** 1. Functional ability value of the Wolf Motor Function Test (WMFT), to assess upper limb functional limitation (score range 0 to 5, higher scores indicate poorer performance) 2. Performance time value of the WMFT, to assesses upper limb functional performance speed (measured in seconds, longer times indicate poorer performance) 3. Quality of Movement (QOM) item in the Motor Activity Log (MAL), to assess how well participants can use their affected upper limb in 30 activities of daily living (score range 0 to 5, lower scores indicate poorer performance)
Notes	**Source of funding:** not reported **Statement regarding declarations of interest:** not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "...we undertook a randomized placebo-controlled study in which stroke patients with CRPSt I were randomly allocated..." Comment: the trial authors did not report the method of sequence generation.
Allocation concealment (selection bias)	Unclear risk	Comment: the trial authors did not report the method of allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: given the nature of the intervention, participants were not blinded to treatment and may have had different expectations about the benefits of each intervention.

Cacchio 2009a *(Continued)*

Blinding of outcome assessment (detection bias) Self-reported outcomes	High risk	Comment: unblinded participants, who may have had different expectations about the benefits of the intervention they received, self-reported some outcomes.
Blinding of outcome assessment (detection bias) Investigator-administered outcomes	Low risk	Quote: "All the patients were examined 3 times by an investigator who was blinded to the nature of treatment performed". Comment: the outcome assessor was blinded to treatment allocation.
Incomplete outcome data (attrition bias) Dropout rate described and acceptable	Unclear risk	Quote: "Two patients (8%) in the mirror group and 7 patients (29%) in the control group dropped out of the study". Quote: "One of the 2 patients in the mirror group dropped out because he moved to another city, while the other decided to perform corticosteroid injection therapy in another center. Three of the 7 patients in the control group refused to complete the study, while 4 decided to perform corticosteroid injection therapy in another center". Comment: the extent to which an overall dropout rate of 19% and an unequal dropout rate between groups may have introduced biased estimates of treatment effect is uncertain.
Incomplete outcome data (attrition bias) Participants analysed in the group to which they were allocated	Low risk	Quote: "Both the primary and secondary outcome analyses were performed according to the intention-to-treat (ITT) principle. In this study, subjects that provided baseline and at least 1 post-treatment measurement constituted the ITT population, whereas those who completed all tests from baseline to the 6-month follow-up constituted the per protocol population." Comment: the trial authors reported analyses according to the ITT principle.
Selective reporting (reporting bias)	Low risk	Comment: the trial authors fully reported outcome data for all outcomes reported in the methods section of the publication.
Sample size	High risk	Quote: "48 patients with CRPSt1 of the affected upper limb were enrolled". Comment: the small sample size may have introduced bias in the estimates of treatment effect.
Duration of follow-up	Low risk	Quote: "The decision to set the follow-up at 6 months is based on the hypothesis that pain improves spontaneously over a long period of time". Comment: the trial authors measured outcomes over a clinically relevant length of time.
Other bias	Low risk	Comment: we did not identify any other sources of bias.

Cacchio 2009b

Study characteristics	
Methods	**Design:** parallel-group, single-blind, 3-arm, sham-controlled RCT. (Whilst the trial authors reported that a number of participants from the 2 comparator groups crossed over into the experimental group, this was not undertaken in a randomised way and therefore we deemed that this trial did not employ a true cross-over design. We analysed it as a 3-arm parallel-group trial up to the endpoint just prior to cross-over). **Setting:** not reported (Italy, dates not reported)

Cacchio 2009b *(Continued)*

	Interventions: mirror therapy or placebo control (covered mirror) or mental imagery
	Sample size calculation: not reported
Participants	**Number of participants:** 24 (8 per group)
	Type of noxious initiating event: stroke (upper limb)
	Diagnostic criteria: Bruehl 1999 (CRPS I)
	Baseline characteristics: not adequately reported
	Inclusion criteria: not explicitly reported
	Exclusion criteria: not reported
Interventions	**Mirror therapy (n = 8)**
	Components of intervention: whilst viewing a reflected image of the unaffected arm in a mirror, participants performed all of the cardinal (proximal to distal) movements of the affected arm (reported as the 'affected' arm but assumed to be the 'unaffected' arm)
	Dosage: 30 minutes per session
	Frequency of administration: daily for 4 weeks (28 sessions)
	Provider: not reported
	Placebo control (n = 8)
	Components of intervention: participants performed the same movements, according to the same dosage and frequency, with the reflective mirror surface covered
	Provider: not reported
	Mental imagery (n = 8)
	Components of intervention: not reported
	Dosage: not reported
	Frequency of administration: not reported
	Provider: not reported
Outcomes	The trial authors assessed outcomes at baseline and on completion of the intervention period (4 weeks post recruitment)
	Primary outcomes:
	1. Self-rated pain intensity on movement using a 100 mm VAS (anchor point labels not reported) but with higher scores indicating more severe pain
	Secondary outcomes:
	1. Motor function as assessed by the Wolf Motor Function Test (WMFT) (scoring properties not reported) 2. Brush-induced allodynia (method of assessment not reported) 3. Oedema (method of assessment not reported)
Notes	**Source of funding:** not reported
	Statement regarding declarations of interest: not reported
Risk of bias	

Cacchio 2009b *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "We conducted a randomised, sham-controlled study involving 24 patients with stroke". Comment: the trial authors did not report the method of sequence generation.
Allocation concealment (selection bias)	Unclear risk	Quote: "We randomly assigned the 24 patients to one of three groups". Comment: the trial authors did not report the method of allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: given the nature of the intervention, participants were not blinded to treatment and may have had different expectations about the benefits of each intervention.
Blinding of outcome assessment (detection bias) Self-reported outcomes	High risk	Comment: unblinded participants, who may have had different expectations about the benefits of the intervention they received, self-reported some outcomes.
Blinding of outcome assessment (detection bias) Investigator-administered outcomes	Low risk	Quote: "The investigators were unaware of the study-group assignments". Comment: outcome assessors were blinded to participants group allocation.
Incomplete outcome data (attrition bias) Dropout rate described and acceptable	Low risk	Quote: "In the active-mirror group, seven of eight patients (88%) reported reduced pain". Quote: "In the covered-mirror group, only one of eight patients (12%) reported reduced pain". Quote: "In the mental-imagery group, two of eight patients (25%) reported reduced pain". Comment: there were no apparent dropouts.
Incomplete outcome data (attrition bias) Participants analysed in the group to which they were allocated	Low risk	Comment: the trial authors analysed participants in the group to which they were allocated but did not report the method of analysis (ITT versus per protocol).
Selective reporting (reporting bias)	High risk	Quote: "After 4 weeks of active mirror therapy, the pain intensity decreased (Fig. 1), and motor function, brush-induced allodynia, and edema improved (data not shown)". Comment: the trial authors presented mean values for the primary outcome of pain severity in graphical format only; they did not report raw data in numerical form with measures of variation. Comment: the trial authors did not report any outcome data for the three secondary outcome measures (motor function, brush-induced allodynia, oedema).
Sample size	High risk	Quote: "We conducted a randomised, sham-controlled study involving 24 patients..." Comment: the small sample size may have introduced bias in the estimates of treatment effect.

Cacchio 2009b *(Continued)*

Duration of follow-up	High risk	Quote: "The primary end point was the score for the severity of pain after 4 weeks of therapy". Comment: the trial authors re-measured outcomes on completion of the intervention period only and did not measure them over a clinically relevant length of time.
Other bias	Unclear risk	Comment: the trial was reported and published as a 'Letter to the Editor'. Full trial methodology and results have not been published elsewhere (Cacchio, personal communication). Comment: the trial authors presented limited group-specific baseline data. Comment: the trial authors did not report any inclusion/exclusion data.

den Hollander 2016

Study characteristics	
Methods	**Design:** parallel-group, 2-arm RCT **Setting:** Department of Rehabilitation at Maastricht University Medical Center (The Netherlands; from January 2009 to June 2013) **Interventions:** exposure in vivo (EXP) or pain-contingent treatment as usual (TAU) **Sample size calculation: "**The square root from this partial eta-squared was used as effect estimator in the software program nQuery Advision 5.0 with alpha 0.05, 2-tailed, and statistical power of 0.80, resulting in 39 participants per condition. Taking into account the duration of the trial, required effort from participants, and dropout rates from previous studies (EXP 33% and TAU 23%), 55 participants per condition was aimed for".
Participants	**Number of participants:** 46 (23 in each group) **Type of noxious initiating event:** aetiology not reported (upper or lower limb) **Diagnostic criteria:** Merskey 1994 (CRPS I) **Baseline characteristics:** 1. EXP: a. Mean (SD) age = 45.83 (11.26) years; female:male = 18:5 b. Mean (SD) duration of CRPS I 5.3 (5.6) years; range (0.33 to 17) c. Upper limb 14, lower limb 8, upper and lower limb 1 2. TAU: a. Mean (SD) age = 43.87 (11.37) years; female:male = 19:4 b. Mean (SD) duration of CRPS I 4.9 (5.4) years; range (0.33 to 20) c. Upper limb 13, lower limb 8, upper and lower limb 2 **Inclusion criteria:** 1. Physiatrist confirmed CRPS I at the time of inclusion 2. Patients reporting at least moderate pain-related fear (mean score of ≥ 34 on the Photographic Series of Daily Activities (PHODA)) **Exclusion criteria:** 1. Patients with CRPS I in both legs or both arms 2. Generalised pain

den Hollander 2016 *(Continued)*

3. Dystonia
4. Pregnancy
5. Severe psychopathology (Symptom Check List-90)
6. Involvement in a litigation procedure regarding CRPS I
7. Insufficient comprehension of Dutch language

Interventions	**Exposure in vivo (n = 23)** Components of intervention: EXP is characterised by repeated exposure to feared movements, activities, and/or sensations to create expectancy violations, resulting in a lowered threat value of these stimuli 1. Session 1: cognitive–behavioural analysis of complaints (pain and its consequences); 2. Session 2: identify movements/activities that are threatening 3. Session 3: education about treatment rationale; completing personalised fear avoidance model 4. Sessions 4 to 17: exposure with behavioural experiments; systematic and repeated exposure to feared movements, activities and/or sensations; catastrophic interpretations regarding these stimuli are challenged and corrected, to lower the threat value of these stimuli Dosage: 1 hour per session Frequency of administration: weeks 1 to 4, 2 sessions per week; weeks 5 to 19, 1 session per week; weeks 10 to 17, 1 session every other week (total 17 hours over 17 sessions) Provider: psychologist and physical or occupational therapist **Pain-contingent treatment as usual (n = 23)** Components of intervention: a standardised physical therapy treatment aimed at increasing control over pain, and optimising coping with CRPS I 1. Session 1: analysis of pain and complaints 2. Session 2: establish the current level of control over pain (low-moderate-high) and explanation of treatment rationale 3. Sessions 3 to 34: depending on the level of control over pain: extinguish source of ongoing pain by rest of the affected limb, connective tissue massage, transcutaneous electric nerve stimulation, exercises aimed at pain reduction, improving skills by practising compensatory strategies, training skills and instructions about body position Dosage: 30 minutes per session Frequency of administration: weeks 1 to 4, 3 sessions per week; weeks 5 to 13, 2 sessions per week; weeks 14 to 17, 1 session per week (total 17 hours over 34 sessions) Provider: physical therapist
Outcomes	Outcomes assessed at baseline, at the end of the treatment period and 6 months post-treatment **Primary outcomes:** 1. Self-reported upper limb disability was measured with the Radboud Skills Questionnaire (RASQ) (score range 0 to 5; higher scores indicate worse disability) (primary outcome) 2. Self-reported lower limb disability was measured with the Walking Ability Questionnaire (WAQ), composed of items from the Walking Ability and the Rising and Sitting Questionnaire (score range 0 to 10; higher scores indicate worse disability) (primary outcome) **Secondary outcomes:** 1. Self-reported pain intensity, measured using the Neuropathic Pain Scale (NPS) (score range 0 to 10; higher scores indicate worse pain) 2. Self-reported pain catastrophising using the Pain Catastrophizing Scale (PCS) (score range 0 to 52; higher scores indicate worse catastrophising about pain)

den Hollander 2016 *(Continued)*

3. Self-reported perceived harmfulness of physical activities, measured using the Perceived Harmfulness of Physical Activities (PHODA) (score range 0 to 100; higher scores indicate greater perceived harmfulness)
4. Health-related quality of life was measured using the Short Form-36 (SF-36) including the Physical Component Scale (PCS) and Mental Component Scale (MCS) (score range 0 to 100; higher score indicate better physical/mental health)

Notes	**Source of funding:** the trial was supported by a grant from Profileringsfonds azM and governmental funding for Maastricht University, Faculty of Psychology. J. W. S. Vlaeyen was also supported by the Odysseus Grant G090208N "The Psychology of Pain and Disability Research Program" funded by the Research Foundation Flanders (FWO Vlaanderen), Belgium, as well as the "Asthenes" long-term structural funding–Methusalem grant by the Flemish Government, Belgium. Funders had no role in study design, data collection, and analysis, decision to publish, or preparation of the manuscript. **Statement regarding declarations of interest:** the authors declared no conflicts of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A computerized "adaptive biased urn randomization" was used to generate a randomization schedule". Comment: the trial authors used an acceptable method to generate the allocation sequence.
Allocation concealment (selection bias)	Low risk	Quote: "This schedule was generated by an independent statistician and was only accessible to 1 researcher who was not involved in the selection, treatment, and measurement." Comment: the trial authors probably used an acceptable method to conceal the allocation sequence.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Participants knew that they would receive 1 of the 2 possible treatments. The content of allocated treatment was revealed in the first treatment session, the content of the other treatment remained unaddressed". Quote: "Research assistants were not informed about treatment assignment. Their coordinating role in receiving data (audiotapes, planning of measurements) made it practically impossible to keep them fully blinded". Quote: "EXP therapists rated EXP a more credible treatment than TAU therapists rated TAU. Although patients rated both treatments equally credible, and our fidelity check confirmed that treatments were delivered according to the protocolized manuals, we do not know if the differential treatment credibility influenced overall quality of treatment delivery, possibly favoring EXP". Comment: given the nature of the intervention, participants and some personnel were not blinded to treatment allocation but the extent to which the lack of blinding may have introduced bias is uncertain.
Blinding of outcome assessment (detection bias) Self-reported outcomes	Low risk	Quote: "Participants knew that they would receive 1 of the 2 possible treatments. The content of allocated treatment was revealed in the first treatment session, the content of the other treatment remained unaddressed". Quote: "...patients rated both treatments equally credible, and our fidelity check confirmed that treatments were delivered according to the protocolized manuals." Comment: the participants were not blinded to treatment allocation and self-reported some outcomes but lack of blinding unlikely to have biased the re-

den Hollander 2016 *(Continued)*

		sults given that participants received interventions judged to have been of relatively equal credibility.
Blinding of outcome assessment (detection bias) Investigator-administered outcomes	Low risk	Not applicable.
Incomplete outcome data (attrition bias) Dropout rate described and acceptable	High risk	Quote: "Three participants did not have any treatment contact (1 EXP, 2 TAU). Eight participants (3 EXP, 5 TAU) did not complete treatment protocol; they were requested to complete further measurements, but only 3 (all TAU) continued testing, resulting in 38 postmeasurements (19 EXP, 19 TAU). At 6-month follow-up, 35 participants (18 EXP, 17 TAU) completed the measurements. Comment: a total dropout rate of 24% (at 6-month follow-up) may have introduced bias in the estimates of treatment effect.
Incomplete outcome data (attrition bias) Participants analysed in the group to which they were allocated	Low risk	Quote: "Data were analyzed using an intention-to-treat approach; no participants were excluded from data analyses". Comment: the trial authors reported analyses according to the ITT principle.
Selective reporting (reporting bias)	High risk	Quote: "Posttreatment assessments were completed within 2 weeks after treatment, at 6-month, and 12-month follow-up. The current report includes posttreatment and 6-month followup data". Comment: data not reported for all time points. Comment: the authors supplied 12-month outcome data for outcomes specified in the trial report on request. Quote: "Physical measures including physical activity in daily life and body function will be reported elsewhere". Comment: the trial authors have not fully reported outcome data for all outcomes. Comment: a number of secondary outcomes outlined, but not fully specified, in the trial registration have not been reported. Comment: measurement of pain intensity using the Neuropathic Pain Scale was reported in the trial report but not the trial registration.
Sample size	High risk	Quote: "We conducted a randomized controlled trial (N = 46) Comment: the small sample size may have introduced bias in the estimates of treatment effect.
Duration of follow-up	Low risk	Quote: "Pretreatment to posttreatment and pretreatment to 6-month follow-up change scores were tested". Comment: the trial authors measured outcomes over a clinically relevant length of time.
Other bias	Low risk	Comment: we did not identify any other sources of bias.

Devrimsel 2015

Study characteristics	
Methods	**Design:** parallel-group, 2-arm RCT **Setting:** not reported (Turkey; dates not reported) **Interventions:** whirlpool bath plus under underwater ultrasound and exercise therapy or neuromuscular electrical stimulation (NMES) plus under underwater ultrasound and exercise therapy **Sample size calculation:** not reported
Participants	**Number of participants:** 60 (30 in each group) **Type of noxious initiating event:** mixed (fracture distal radius n = 33, fracture metacarpal n = 9, tendon injury n = 18) (upper limb) **Diagnostic criteria:** Harden 2010 (CRPS I) **Baseline characteristics:** 1. Whirlpool bath: a. Mean (SD) age = 38.86 (9.76) years; female:male 18:12 b. Mean (SD) duration of CRPS I weeks (SD) = 5.46 (0.73) weeks 2. NMES: a. Mean (SD) age = 40.20 (9.08) years; female:male 17:13 b. Mean (SD) duration of CRPS I (weeks) = 5.11 (0.73) weeks **Inclusion criteria:** 1. Diagnosis of CRPS I **Exclusion criteria:** 1. Patients with peripheral neuropathy or a nerve lesion 2. A history of hand fracture 3. Systemic disease (e.g. diabetes mellitus, infection, or tumour) 4. An open hand wound
Interventions	Participants in both groups received i) underwater ultrasound therapy (performed by placing the ultrasound probe 1 to 2.5 cm away from the hand and wrist underwater; treatment intensity was 1.5 W/cm^2, and the probe was slowly moved parallel to the treatment area for 5 minutes; ii) exercise therapy (joint range of motion and stretching up to each patient's pain threshold, further details not reported); each for 5 days per week for 3 weeks), and iii) were allowed to take paracetamol (500 mg, 3 times per day) **Whirlpool bath (n = 30)** Components of intervention: treatment was administered using a Chiron extremity caldron device (Chirana Progress, Slovakia). The water temperature was set at 40 °C and monitored with a thermometer. Hands and wrists were positioned in the most comfortable resting position that would not impede perfusion and placed in the water tank. Dosage: 30 minutes Frequency of administration: 5 days per week for 3 weeks (total 15 sessions) Provider: not reported **NMES (n = 30)** Components of intervention: treatment was administered using a Cefar device (Cefar, European Union) Dosage: symmetrical biphasic current pulses were applied at a 30 Hz frequency for 300 ms. Each muscle group (flexor and extensor muscle groups) was treated for 20 minutes

Devrimsel 2015 *(Continued)*

	Frequency of administration: 5 days per week for 3 weeks (total 15 sessions) Provider: not reported
Outcomes	Outcomes assessed at baseline and on completion of the intervention period. 1. Self-reported pain measured using a 10 cm VAS (0 = no pain, 10 = worst pain) 2. Hand grip strength (HGS) measured using a hand dynamometer (Jamar, USA) (mean of 3 measurements; in kg) 3. Pinch strength (fingertip grip (FGS), three-point grip (TPGS), and lateral grip (LGS)) measured using a manual pinch meter (Jamar, Sammons Preston, Inc. Bolingbrook, IL, USA) (mean of 3 measurements; in kg) 4. Upper limb oedema measured using volumetric measurements of water displacement (in ml) 5. Wrist flexion and wrist extension were measured with a hand goniometer 6. Finger-to-palm crease distance (in cm)
Notes	**Source of funding:** not reported **Statement regarding declarations of interest:** not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were randomized into two 30-patient groups". Comment: the trial authors did not report the method of sequence generation.
Allocation concealment (selection bias)	Unclear risk	Comment: the trial authors did not report the method of allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: participants were not blinded to treatment allocation but a lack of blinding is unlikely to have biased the results given that participants received interventions judged to have been of relatively equal credibility.
Blinding of outcome assessment (detection bias) Self-reported outcomes	Low risk	Comment: participants were not blinded to treatment allocation but a lack of blinding is unlikely to have biased the results given that participants received interventions judged to have been of relatively equal credibility.
Blinding of outcome assessment (detection bias) Investigator-administered outcomes	Unclear risk	Comment: the trial authors did not give a statement of procedures regarding blinding of the outcome assessor.
Incomplete outcome data (attrition bias) Dropout rate described and acceptable	Unclear risk	Comment: the dropout rate was not reported.
Incomplete outcome data (attrition bias) Participants analysed in the group to which they were allocated	Unclear risk	Comment: the method of analysis (ITT versus per protocol) was not reported.
Selective reporting (reporting bias)	Low risk	Comment: outcome data were adequately reported for all outcomes reported in the methods section of the publication.

Devrimsel 2015 *(Continued)*

Sample size	High risk	Quote: "Sixty outpatients (30 per group) with complex regional pain syndrome participated". Comment: the small sample size may have introduced bias in the estimates of treatment effect.
Duration of follow-up	High risk	Quote: "All parameters were measured at baseline (week 0) and at the trial end (week 3)". Comment: the trial authors did not measure outcomes over a clinically relevant length of time.
Other bias	Low risk	Comment: we did not identify any other sources of bias.

Dimitrijevic 2014

Study characteristics	
Methods	**Design:** parallel-group, 2-arm, single-blind RCT **Setting:** outpatient clinic (Serbia; December 2004 to January 2007) **Interventions:** low-level laser therapy and kinesitherapy or interferential current therapy and kinesitherapy **Sample size calculation:** not reported
Participants	**Number of participants:** 50 (25 per group) **Type of noxious initiating event:** trauma (no further details reported) (upper and lower limb) **Diagnostic criteria:** Harden 2005 (CRPS I) **Baseline characteristics:** 1. laser therapy and kinesitherapy: a. Mean (±) age = 53.9 (13.36) years; female:male = 12:8 b. Mean (±) duration of CRPS I 33.75 (8.44) days 2. interferential current therapy and kinesitherapy: a. Mean (±) age = 57.8 (10.75) years; female:male = 17:8 b. Mean (±) duration of CRPS I = 31.64 (7.79) days **Inclusion criteria:** 1. CRPS I **Exclusion criteria:** 1. Acute and subacute thrombophlebitis 2. Thrombosis 3. Neoplastic disease 4. Fever 5. Pregnancy
Interventions	Participants were instructed not to take any specific CRPS medication (corticosteroids, bisphosphonates, calcitonin, nifedipine, antiepileptic drugs, etc.) or analgesic medication. Participants in both groups received individual kinesitherapy (active and active assisted exercises, strictly dosed up to pain threshold) for 30 minutes, twice a day.

Dimitrijevic 2014 *(Continued)*

	Low-level laser therapy and kinesitherapy (n = 20) Components of intervention: using a GaAs laser diode, 8 points along the joint line and painful points in the affected area were treated using the following parameters: a low power of 70 mW, 810 nm wavelength, and 70 Hz, 640 Hz and 5000 Hz frequency, depending on the dominant findings Dosage: 1.5 J/cm^2 Frequency of administration: 5 days a week for 2 weeks (10 sessions), and then every other day (10 sessions) (20 sessions) Provider: not reported **Interferential current therapy and kinesitherapy (n = 25)** Components of intervention: bipolar IFC therapy was applied with electrodes positioned locally on the painful and swollen part using the following parameters: 90 Hz frequency Dosage: 15 minutes Frequency of administration: 5 days a week for 2 weeks (10 sessions), and then every other day (10 sessions) (20 sessions) Provider: not reported
Outcomes	The trial authors did not explicitly specify the time points at which outcomes were measured in the trial report. Outcomes assessed at baseline and on completion of the intervention period (6 weeks post recruitment) (Dimitrijevic, personal communication). The trial authors did not state any primary outcome. 1. Self-rated pain intensity at rest using a 100 mm horizontal VAS (0 = no pain, 100 = worst pain possible) with responses based on the average pain intensity over last few days 2. Self-rated pain intensity during active movements of the wrist/ankle using a 100 mm horizontal VAS (0 = no pain, 100 = worst pain possible) with responses based on the average pain intensity over last few days 3. Oedema of the hand/foot using a figure-of-8 measurement (measurement tool and method not reported). Hand/foot oedema was expressed as the difference between hand/foot circumference of the affected and unaffected sides 4. Total active range of motion of the wrist/ankle joint in the sagittal plane using a standard full-circle goniometer and recorded in degrees with the final value derived from mean of 3 measurements
Notes	**Source of funding:** the trial authors declared that this study received no financial support **Statement regarding declarations of interest:** none declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "...patients were randomly selected and classified into two groups using sequentially numbered, closed, opaque envelopes that had been prepared earlier using a computer-generated list of random numbers, and balanced to ensure equal numbers in each group". Comment: the trial authors used an acceptable method to generate the allocation sequence.
Allocation concealment (selection bias)	Low risk	Quote: "...patients were randomly selected and classified into two groups, using sequentially numbered, closed, opaque envelopes that had been prepared earlier".

Dimitrijevic 2014 *(Continued)*

		Comment: the trial authors used an acceptable method to conceal the allocation sequence.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: the participants were not blinded to treatment allocation but lack of blinding unlikely to have biased the results given that participants received interventions judged to have been of relatively equal credibility.
Blinding of outcome assessment (detection bias) Self-reported outcomes	Low risk	Comment: the participants were not blinded to treatment allocation and self-reported some outcomes but lack of blinding unlikely to have biased the results given that participants received interventions judged to have been of relatively equal credibility.
Blinding of outcome assessment (detection bias) Investigator-administered outcomes	Unclear risk	Comment: the trial authors did not provide a statement of procedures regarding blinding of the outcome assessor.
Incomplete outcome data (attrition bias) Dropout rate described and acceptable	Unclear risk	Quote: "During the study, 5 out of 50 patients dropped out. A total of 45 patients completed the study". Comment: all 5 dropouts came from the laser therapy group (lost to follow-up, n = 2; discontinued intervention, n = 3). Whilst the overall dropout rate was 10%, the extent to which an unequal dropout rate between groups may have biased the results is uncertain.
Incomplete outcome data (attrition bias) Participants analysed in the group to which they were allocated	High risk	Comment: the trial authors excluded 3 participants from the laser therapy group from the analysis because they discontinued the intervention, in violation of the ITT principle.
Selective reporting (reporting bias)	Low risk	Comment: the trial authors fully reported outcome data for all outcomes reported in the methods section of the publication.
Sample size	High risk	Quote: "The prospective randomized study included 50 patients with unilateral post-traumatic CRPS I". Comment: the small sample size may have introduced bias in the estimates of treatment effect.
Duration of follow-up	High risk	Quote: "All patients underwent evaluation of each separate parameter before treatment and after applying 20 therapeutic procedures". Comment: outcomes were re-measured on completion of the intervention period only and were not measured over a clinically relevant length of time.
Other bias	Low risk	Comment: we did not identify any other sources of bias.

Duman 2009

Study characteristics	
Methods	**Design:** parallel-group, 2-arm RCT **Setting:** not reported (Turkey; dates not reported) **Interventions:** conventional care plus manual lymphatic drainage (MLD) or conventional care

Duman 2009 *(Continued)*

	Sample size calculation: not reported
Participants	**Number of participants:** 34 (experimental group n = 18, control group n = 16) **Type of noxious initiating event:** mixed (fracture n = 23, soft tissue trauma n = 7, incisive injury n = 3, non-traumatic n = 1) (upper limb) **Diagnostic criteria:**Bruehl 1999 (RSD i.e. CRPS I) **Baseline characteristics:** Total sample (separate intervention and control group data not reported but no statistically significant between-group differences). Mean (±) age = 20.6 (0.8) years; female:male = not reported Mean (±) duration of reflex sympathetic dystrophy (RSD) 5.1 (1.3) months **Inclusion criteria:** 1. Fulfilled IASP criteria for RSD 2. Minimum 50 cc volumetric difference between 2 upper limbs **Exclusion criteria:** 1. Infection 2. Thrombosis 3. Cardiac, pulmonary or renal problems
Interventions	Participants in both groups received conventional care including non-steroidal anti-inflammatory drugs (NSAIDs) (type, dosage, frequency of administration not reported) and physical therapy (once per day, 5 days per week for 3 weeks), comprising therapeutic ultrasound of the affected limb and stellate ganglions (treatment parameters not reported) and therapeutic exercises for all joints of the affected limb (10 repetitions, twice per day; type of exercises performed not reported) followed by a 2-month programme of home maintenance therapeutic exercises. **MLD (n = 18)** Components of intervention: MLD. Light massage for superficial abdominal, axillary and upper limb lymphatic stimulation of the affected upper limb followed by light upper limb massage in a distal to proximal direction up to the axillary region. Dosage: 1 session per day for approximately 45 minutes administered by a therapist plus 1 session per day of participant self-administered MLD (duration not reported). Frequency of administration: 5 times per week for 3 weeks (15 sessions), followed by a home maintenance programme of self-administered MLD for 2 months Provider: not reported **Conventional care (n = 16)**
Outcomes	Outcomes assessed at baseline, at the end of the 3-week treatment period and 2 months post-treatment. The trial authors did not state any primary outcome. 1. Self-rated pain intensity during gentle passive finger flexion using a 10 cm VAS labelled "no pain" to "worst possible pain" 2. Upper limb oedema using volumetric measurements of water displacement 3. Functional range of motion measuring the third finger pulp-distal palmer crease distance
Notes	**Source of funding:** not reported

Duman 2009 *(Continued)*

Statement regarding declarations of interest: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The patients were allocated randomly into two groups". Comment: the trial authors did not report the method of sequence generation.
Allocation concealment (selection bias)	Unclear risk	Comment: the trial authors did not report the method of allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: given the nature of the intervention, participants were not blinded to treatment and may have had different expectations about the benefits of each intervention.
Blinding of outcome assessment (detection bias) Self-reported outcomes	High risk	Comment: unblinded participants, who may have had different expectations about the benefits of the intervention they received, self-reported some outcomes (e.g. pain intensity).
Blinding of outcome assessment (detection bias) Investigator-administered outcomes	Unclear risk	Quote: "All of the parameters were obtained before the treatment (baseline), after treatment and 2 months after treatment (follow-up) by a different physician". Comment: the trial authors did not report a statement of procedures regarding blinding of the outcome assessor.
Incomplete outcome data (attrition bias) Dropout rate described and acceptable	Low risk	Quote: "After 2 months, all of the patients were re-evaluated". Comment: there were no apparent dropouts.
Incomplete outcome data (attrition bias) Participants analysed in the group to which they were allocated	Low risk	Quote: "After 2 months, all of the patients were re-evaluated". Comment: trial authors analysed participants analysed in the group to which they were allocated but did not report the method of analysis (ITT versus per protocol).
Selective reporting (reporting bias)	Low risk	Comment: the trial authors fully reported outcome data for all outcomes reported in the methods section of the publication.
Sample size	High risk	Quote: "A total of 34 patients who fulfilled the modified International Association for the Study of Pain (IASP) criteria and diagnosed as RSD were enrolled". Comment: the small sample size may have introduced bias in the estimates of treatment effect.
Duration of follow-up	Low risk	Quote: "After 2 months, all of the patients were re-evaluated". Comment: the trial authors measured outcomes over a clinically relevant length of time.
Other bias	Low risk	Comment: we did not identify any other sources of bias.

Durmus 2004

Study characteristics	
Methods	**Design:** parallel-group, 2-arm, double-blind, placebo-controlled RCT **Setting:** out-patient rehabilitation clinic (Turkey; 1999 to 2001) **Interventions:** usual care plus pulsed electromagnetic field treatment or usual care plus placebo pulsed electromagnetic field treatment **Sample size calculation:** not reported
Participants	**Number of participants:** 40 (number of participants per group not reported) **Type of noxious initiating event:** Colles fracture (upper limb) **Diagnostic criteria:** Merskey 1994 (CRPS I) **Baseline characteristics:** 1. Pulsed electromagnetic field treatment: a. Mean (SD) age = 37.65 (12.33) years; female:male = 50%:50% b. Mean (SD) duration of CRPS I: 48.80 (28.63) days 2. Placebo: a. Mean (SD) age = 40.60 (11.05) years; female:male = 45%:55% b. Mean (SD) duration of CRPS I: 54.55 (36.24) days **Inclusion criteria:** 1. Aged 18 to 55 years 2. Development of pathology after trauma 3. Presence of phase I CRPS I based on 3 phase bone scintigraphy 4. Absence of any known hypersensitivities to calcitonin **Exclusion criteria:** 1. Previous treatment for CRPS I 2. Pacemaker 3. Presence of an infectious or malignant disease 4. Being either pregnant or in a menopausal state
Interventions	Participants in both groups received 100 units of calcitonin via intramuscular injection for 6 weeks; once per day for the first 3 weeks then once every other day for the second 3 weeks, and performed active and active assisted range of motion exercises and a stretching programme for 30 minutes, 3 times per day. **Electromagnetic field treatment (n = not reported)** Components of intervention: pulsed electric magnetic field treatment. Treatment was administered using a Magnetic-Therapy Mg Port Cosgamma® device. The trial authors did not report participant and equipment positioning. Dosage: 100 Gauss intensity and 50 Hz frequency for 60 minutes per session Frequency of administration: 5 times per week for 6 weeks (30 sessions) Provider: not reported **Placebo (n = not reported)** Components of intervention: participants were placed in the same device without it being switched on

Durmus 2004 *(Continued)*

Outcomes	The trial authors assessed outcomes at baseline and on completion of the intervention period (6 weeks post recruitment). The trial authors did not state any primary outcome. 1. Self-rated pain at rest using a 10 cm VAS graded between 0 and 10 (anchor point descriptors not reported) 2. Self-rated pain with activity (details not reported) using a 10 cm VAS graded between 0 and 10 (anchor point descriptors not reported) 3. 4-point verbal pain scale (measurement properties not described) 4. Pain on palpation using 5-point grading scale (0 = no pain, 4 = hyperaesthesia) (further measurement properties not reported) 5. Ratings of stiffness and change of colour (measurement properties not reported) 6. Change in oedema using volumetric displacement 7. Range of motion using a goniometer (joints not specified) 8. 3-phase bone scintigraphy (bone to soft-tissue ratios) (measurement properties not reported) 9. Biochemical markers of bone formation (bone alkaline phosphatase, osteocalcin, procollagen 1) and bone resorption (pyridinoline, deoxypyridinoline, hydroxyproline) (measurement properties not reported)
Notes	**Source of funding:** not reported **Statement regarding declarations of interest:** not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The patients were divided into two groups with the random numbers table". Comment: the trial authors used an acceptable method to generate the allocation sequence.
Allocation concealment (selection bias)	Unclear risk	Comment: the trial authors did not report the method of allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "In this randomized double-blind, placebo-controlled study". Quote: "the second group of patients received placebo treatment by being placed in the same device without it being switched on". Comment: participants were likely to have been adequately blinded but the trial authors did not explicitly report the extent to which the placebo intervention controls for the auditory and sensory characteristics of the intervention. Comment: the trial authors did not report the procedure for blinding of care providers.
Blinding of outcome assessment (detection bias) Self-reported outcomes	Low risk	Quote: "the second group of patients received placebo treatment by being placed in the same device without it being switched on". Comment: the participants who completed self-reported outcome measures were blinded to treatment allocation.
Blinding of outcome assessment (detection bias) Investigator-administered outcomes	Low risk	Quote: "The patients were assessed at the beginning of a 6 week course of treatment and on the final week of treatment by a physician who did not know which group received the applied magnetic field treatment". Comment: the outcome assessor was blinded to treatment allocation.

Durmus 2004 *(Continued)*

Incomplete outcome data (attrition bias) Dropout rate described and acceptable	Low risk	Quote: "There were no refusals or drop-outs from the study". Comment: all randomly assigned participants completed the study.
Incomplete outcome data (attrition bias) Participants analysed in the group to which they were allocated	Low risk	Quote: "There were no refusals or drop-outs from the study". Comment: the trial authors did not report the method of analysis (ITT versus per protocol).
Selective reporting (reporting bias)	High risk	Comment: the trial authors fully reported outcome data for the 2 main pain outcomes but did not report any outcome data for the 4-point verbal pain scale or any other outcomes (pain on palpation, ratings of stiffness and change of colour, range of motion and 3-phase bone scintigraphy), as reported in the methods section of the publication.
Sample size	High risk	Quote: "Forty patients diagnosed as having Type I CRPS subsequent to trauma (Colles Fracture), who consulted the Physical Medicine and Rehabilitation Department of Istanbul University, Istanbul Medical Faculty between 1999 and 2001 were included in the study". Comment: the small sample size may have introduced bias in the estimates of treatment effect.
Duration of follow-up	High risk	Quote: "Patients were assessed at the beginning of a 6 week course of treatment and on the final week of treatment". Comment: the trial authors re-evaluated participants at the end of the treatment period only.
Other bias	Low risk	Comment: we did not identify any other sources of bias.

Halicka 2021

Study characteristics	
Methods	**Design:** parallel-group, 2-arm, double-blind RCT **Setting:** university clinics and patients' homes (United Kingdom; March 2017 to July 2019) **Interventions:** prism adaptation treatment or sham prism adaptation treatment **Sample size calculation:** 21 participants per treatment group required to provide 90% power to detect a minimal clinically significant reduction of 2 on the primary outcome of pain intensity (0 to 10 NRS), with a SD of 1.98, and a 2-tailed alpha of 0.05
Participants	**Number of participants:** 52 (26 per group) (N.B. 3 participants dropped out after randomisation and during the baseline assessment process. The following data are for n = 49). **Type of noxious initiating event:** mixed (hand surgery n = 3, hand soft tissue injury n= 3, finger fracture n = 3, arm fracture n = 3, wrist sprain n = 5, finger soft tissue injury n = 4, wrist fracture n = 8, elbow fracture n = 2, wrist surgery n = 2, shoulder whiplash injury n = 2, arm soft tissue injury n = 2, shoulder surgery n = 1, breast surgery n = 1, elbow soft tissue injury n = 1, heart surgery n = 1, hand surgery n = 1, arm fracture n = 1, shoulder dislocation n = 2, none n = 4) (upper limb). (N.B. multiple inciting events were reported for many participants. 'Initiating events' have been categorised according to the first event in the list for simplicity).

Halicka 2021 *(Continued)*

Diagnostic criteria: 'Budapest criteria' Harden 2010 (CRPS I)

Baseline characteristics:

1. Prism adaptation treatment:
   a. Mean age = 47.35 (range 43.20 to 51.95) years; female:male = 83%:17%
   b. Mean duration of CRPS I: 61.26 (range 47.15 to 75.12) months
2. Sham prism adaptation treatment:
   a. Mean age = 45.31 (range 39.85 to 50.85) years; female:male = 85%:15%
   b. Mean duration of CRPS I: 52.31 (range 39.49 to 66.35) months

Inclusion criteria:

1. Aged 18 to 80 years
2. Diagnosis of CRPS-I primarily affecting one upper limb based on the Budapest research criteria for ≥ 3 months
3. Current pain intensity of ≥ 2 on a 0 to 10 NRS

Exclusion criteria:

1. Lacking sufficient English language ability to provide informed consent
2. Legally blind
3. History of a neurological disorder
4. CRPS in the opposite limb meeting the Budapest clinical or research criteria
5. Confirmed nerve damage (CRPS-II)
6. Reporting or showing dystonia or other physical impairment preventing satisfactory execution of interventions
7. Severe psychiatric comorbidity that could be associated with perceptual changes

Interventions

Participants in both groups were instructed to continue any usual treatments (including medications) but were asked not to change their treatment regimens throughout the duration of the trial if possible.

Prism adaptation treatment (n = 23)

Participants used welding goggles fitted with 35-diopter Fresnel lenses that induced approximately 19° optical deviation away from the CRPS-affected side. Participants were seated approximately 50 cm from a wall and an A4 sheet was positioned on the wall in landscape orientation at eye-level and aligned with their body midline. There were 2 targets (2 cm-diameter red circles) on the sheet, located 12.5 cm to the left and 12.5 cm to the right of the participant's body midline. While wearing the prism goggles, participants used their CRPS-affected arm to perform 50 pointing movements, as fast as possible, alternating between the left and right target. The welding goggles occluded the first half of the arm movement and participants were encouraged to point as quickly as possible. Participants were instructed to perform self-guided treatment sessions at home.

Dosage: (duration of each session) not reported

Frequency of administration: 2 times per day for 2 weeks (29 sessions)

Provider: research psychologists

Sham prism adaptation treatment (n = 26)

Participants carried out exactly the same procedure as the active group, except the welding goggles used were fitted with neutral lenses that did not induce any lateral shift. The neutral lenses distorted the acuity and clarity of vision to a similar extent as prism lenses.

Dosage: not reported

Frequency of administration: 2 times per day for 2 weeks (29 sessions)

Provider: research psychologists

Halicka 2021 *(Continued)*

Outcomes	Outcomes assessed over 2 baseline sessions (3 to 4 weeks before randomisation and 1 to 5 days before the commencement of treatment), on completion of the treatment period (primary endpoint), and then 4 weeks, 3 months and 6 months post-treatment. Primary outcomes: 1. Self-reported pain intensity using an 11-point NRS ranging from 0 (no pain) to 10 (pain as bad as you can imagine) 2. The CRPS Severity Score consisting of 8 self-reported symptoms and 8 signs evaluated upon clinical valuation scored as 0 (absent) or 1 (present); the summed score ranges from 0 to 16 with higher scores indicating greater CRPS severity Secondary outcomes: 1. Self-reported pain intensity and pain interference assessed using the Brief Pain Inventory, comprising 2 x 0 to 10 subscales, with higher scores indicating greater pain intensity/interference 2. Self-reported neuropathic features of pain using the Pain Detect Questionnaire, comprising a -1 to 38 scale, with higher scores indicating a greater neuropathic component of experienced pain 3. Self-reported body representation using the Bath CRPS Body Perception Disturbance Scale, comprising a 0 to 57 scale, with higher scores indicating greater distortions 4. Self-reported emotional functioning using the Tampa Scale for Kinesiophobia, comprising a 17 to 68 scale, with higher scores indicate more severe pain-related fear of movement and re-injury 5. Self-reported Profile of Mood states, comprising a 17 to 229 scale, with higher scores indicating greater mood disturbance 6. Self-reported Patient Global Impression of Change Questionnaire, comprising a 1 to 7 scale, with higher scores indicating greater treatment-related improvement in the domains of activity limitations, symptoms, emotions and overall quality of life related to CRPS N.B. trial authors assessed a range of additional measures of sensory function (quantitative sensory testing, two-point discrimination thresholds), autonomic and motor function (temperature difference, oedema, grip strength,delta finger-to-palm distance) and neuropsychological functions (visuospatial attention in near space (Temporal Order Judgement, Landmark, and Greyscales tasks), mental representation of space (Mental Number Line Bisection task), spatially defined motor function, and body representation (Hand Laterality Recognition task)) not further detailed here.
Notes	**Source of funding:** The study was supported by a grant from the Reflex Sympathetic Dystrophy Syndrome Association (RSDSA) awarded to JHB and MJP. The RSDSA approved the design of the study. The funders had no role in data collection and analysis, decision to publish, or preparation of the manuscript. **Statement regarding declarations of interest:** "MH and ADV were supported by studentships from the University of Bath and the GW4 BioMed Medical Research Council Doctoral Training Partnership (ref. 1793344), respectively". 2 authors have received support from the Pain Relief Foundation, Liverpool, 3 authors are committee members of the CRPS UK Research Network, and 1 author is a committee member of the Physiotherapy Pain Association and the British Pain Society. The authors have no other competing interests to declare.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Participants were randomly assigned to either PA or sham treatment group with equal allocation ratio, using MINIM software". Comment: the trial authors used an acceptable method to generate the allocation sequence.
Allocation concealment (selection bias)	Unclear risk	Quote: "The researcher responsible for enrolment and all data collection remained blinded to participants' treatment allocation".

Halicka 2021 *(Continued)*

		Comment: the trial authors did not adequately report the method of allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The participants were blinded to their treatment allocations throughout the entire duration of the trial". Quote: "The only researchers who were aware of individual treatment allocations were those who randomised the participants and/or trained them in carrying out PA or sham treatments and provided them with prism or neutral goggles". Comment: the participants and personnel were blinded to treatment allocation.
Blinding of outcome assessment (detection bias) Self-reported outcomes	Low risk	Quote: "The participants were blinded to their treatment allocations throughout the entire duration of the trial". Quote: "Only 12% of participants in each group correctly guessed their treatment allocation, therefore participant blinding was successful". Comment: the participants who completed self-reported outcome measures were blinded to treatment allocation.
Blinding of outcome assessment (detection bias) Investigator-administered outcomes	Low risk	Quote: "The researcher responsible for enrolment and all data collection remained blinded to participants' treatment allocation". Comment: the outcome assessor was blinded to treatment allocation.
Incomplete outcome data (attrition bias) Dropout rate described and acceptable	High risk	Quote: "Eight participants (16%) withdrew from the study following treatment allocation". Comment: The trial's CONSORT diagram shows i) an additional 4 participants (2 in each group) were lost secondary to 'loss of contact, giving an overall dropout rate of 24%, and ii) the dropout rate was uneven between groups (n = 4 in the prism adaptation group, n = 8 in the sham prism adaptation group). Comment: a total dropout rate of 24% (at 6-month follow-up) may have introduced bias in the estimates of treatment effect.
Incomplete outcome data (attrition bias) Participants analysed in the group to which they were allocated	High risk	Quote: "Our primary analysis involved the intention-to-treat population, that is, participants who received their allocated intervention (i.e. received in-person training immediately after RS2), regardless of their treatment adherence or completion of the outcome assessments (PA treatment = 23, sham treatment = 26). Note that the trial protocol defined this population as all participants allocated to treatment, which did not account for the possibility that they could withdraw before being trained in how to carry out their allocated intervention. This was the case for three participants who were not included in the intention-to-treat sample as per an updated definition". Comment: the trial authors violated the ITT principle.
Selective reporting (reporting bias)	Low risk	Comment: the trial authors reported incomplete outcome data (no measures of variance) for all outcomes reported in the methods section of the manuscript. Comment: the authors supplied these missing data for our outcomes of interest on request.
Sample size	High risk	Quote: "Forty-nine eligible adults with CRPS were randomized to undergo two-weeks of twice-daily home-based prism adaptation treatment (n = 23) or sham treatment (n = 26)".

Halicka 2021 *(Continued)*

		Comment: the small sample size may have introduced bias in the estimates of treatment effect.
Duration of follow-up	Low risk	Quote: "Long-term postal follow-ups were conducted three and six months after treatment". Comment: the trial authors measured outcomes over a clinically relevant length of time.
Other bias	Low risk	Comment: we did not identify any other sources of bias.

Hazneci 2005

Study characteristics	
Methods	**Design:** parallel-group, 2-arm RCT **Setting:** Department of Physical Medicine and Rehabilitation Clinic, Gulhane Military Medical Academy (Turkey; 2001 to 2002) **Interventions:** transcutaneous electrical nerve stimulation (TENS) or pulsed ultrasound of the stellate ganglion **Sample size calculation:** not reported
Participants	**Number of participants:** 30 (TENS N = 16; pulsed ultrasound N = 14) **Type of noxious initiating event:** mixed (trauma n = 20, sports injury n = 5, post finger amputation n = 1, post injection n = 1, idiopathic n = 3) (upper limb) **Diagnostic criteria:** Kozin 1992 (stage I and II) (reflex sympathetic dystrophy syndrome) **Baseline characteristics** 1. TENS: a. Mean (SD) age = 20.75 (0.58) years; female:male = 0:16 b. Mean (SD) duration of CRPS I 45.31 (26.68) days 2. Pulsed ultrasound of the stellate ganglion: a. Mean (SD) age = 20.6 (0.76) years; female:male = 0:14 b. Mean (SD) duration of CRPS I 43.21 (17.72) days **Inclusion criteria:** CRPS I **Exclusion criteria:** not reported
Interventions	Participants in both groups received contrast bathing (the upper extremity was put in hot water for 4 minutes and then in cold water for 1 minute and this procedure was repeated for 20 minutes) and an exercise programme (undertaken with the assistance of a physiotherapist and comprising active, assisted active and passive exercise within the pain limits; including extension, flexion, ulnar and radial deviation for the wrist, abduction and flexion for the thumb, flexion and extension for the metacarpophalangeal, proximal and distal interphalangeal joints). **TENS (n = 16)** Components of intervention: TENS was applied, using a Myomed 932 Enraf model, to the painful area of the involved upper extremity Dosage: frequency 100 Hz, mono-rec wave module

Hazneci 2005 *(Continued)*

	Frequency of administration: once per day, for 20 minutes, for 3 weeks (total number of sessions not reported) Provider: not reported **Pulsed ultrasound of the stellate ganglion (n = 14)** Components of intervention: using a BTL 07p model ultrasound device pulsed ultrasound was applied with a 1 cm^2 probe to the stellate ganglion on the involved side of the upper extremity Dosage: 3 watt/cm^2 (pulsed) Frequency of administration: once per day, for 5 minutes, for 3 weeks (total number of sessions not reported) Provider: not reported
Outcomes	The trial authors assessed outcomes at baseline and on completion of the intervention period (3 weeks post recruitment): 1. Self-reported spontaneous pain measured using a VAS (0 = no pain to 10 = worst pain) 2. Self-reported provocative pain (pain on palpation) measured using a Likert-type scale (0 = no pain, 1 = mild pain with deep palpation, 2 = severe pain with deep palpation, 3 = severe pain with superficial palpation, 4 = hyperaesthesia) 3. Grip strength measured using a hand dynamometer device with the score (in kg) determined by the mean of 3 attempts 4. Joint mobility (extension, flexion, ulnar and radial deviation of the wrist; flexion and extension for the fingers). Active joint movement distance was measured by standard goniometer. Mobility loss was calculated by the formula: 100 − (measured value/normal joint movement distance) x 100. The mean value for the joint movement distance for all directions was calculated and compared with the values of the normal extremity. The scale was as follows: 0 = total mobility; 1 = 1% to 25% mobility loss; 2 = 26% to 50% mobility loss; 4 = mobility loss of more than 76%. 5. Oedema measured using standard volumetric measurements. Firstly the participant's uninvolved upper extremity was placed in a container filled with water. The volume (in mL) of displaced water was measured and compared to the volume displaced when he involved upper extremity was placed in the same container with the value taken as the difference between the volumes displaced by the affected and normal extremities.
Notes	**Source of funding:** not reported **Statement regarding declarations of interest:** not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were divided into two groups randomly". Comment: the trial authors did not report the method of sequence generation.
Allocation concealment (selection bias)	Unclear risk	Comment: the trial authors did not report the method of allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: the participants appear not to have been blinded to treatment allocation but lack of blinding is unlikely to have biased the results given that participants received interventions judged to have been of relatively equal credibility.
Blinding of outcome assessment (detection bias) Self-reported outcomes	Low risk	Comment: participants appear not to have been blinded to treatment allocation and self-reported some outcomes, but lack of blinding is unlikely to have

Hazneci 2005 *(Continued)*

		biased the results given that participants received interventions judged to have been of relatively equal credibility.
Blinding of outcome assessment (detection bias) Investigator-administered outcomes	Unclear risk	Comment: the trial authors did not give a statement of procedures regarding blinding of the outcome assessor.
Incomplete outcome data (attrition bias) Dropout rate described and acceptable	Unclear risk	Comment: the trial authors did not report the dropout rate.
Incomplete outcome data (attrition bias) Participants analysed in the group to which they were allocated	Unclear risk	Comment: the trial authors did not report the method of analysis (ITT versus per protocol).
Selective reporting (reporting bias)	Low risk	Comment: the trial authors fully reported outcome data for all outcomes reported in the methods section of the publication.
Sample size	High risk	Quote: "30 patients diagnosed with Reflex Sympathetic Dystrophy Syndrome at the upper extremities were included into the study". Comment: the small sample size may have introduced bias in the estimates of treatment effect.
Duration of follow-up	High risk	Quote: "All patients evaluated before treatment and 3rd week following the treatment" Comment: the trial authors re-measured outcomes on completion of the intervention period only and they were not measured over a clinically relevant length of time.
Other bias	Low risk	Comment: we did not identify any other sources of bias.

Hwang 2014

Study characteristics	
Methods	**Design:** parallel-group, 3-arm RCT **Setting:** tertiary pain management centre in Seoul (South Korea; dates not reported) **Interventions:** 'virtual body swapping with mental rehearsal' (VBS) or 'watching movement only' (WM) or 'mental rehearsal only' (MR) **Sample size calculation:** not reported
Participants	**Number of participants:** 39 (13 in each group) **Type of noxious initiating event:** not reported (upper and lower limb) **Diagnostic criteria:** Bruehl 1999 (CRPS I and II) **Baseline characteristics:** 1. VBS:

Hwang 2014 *(Continued)*

a. Mean (± SD) age = 36.31 (1.90) years; female:male = 7.7%:92.3%
b. Median (range) duration of pain (months) 66 (25 to 120)
c. Major pain site (%) upper limb = 53.8, lower limb = 30.8, both = 15.4

2. WM:
   a. Mean (± SD) age = 43.00 (2.79) years; female:male = 38.5%:61.5%
   b. Median (range) duration of pain (months) 39 (12 to 158)
   c. Major pain site (%) upper limb = 35.8, lower limb = 30.8, both = 30.8
3. MR:
   a. Mean (± SD) age = 43.08 (2.38) years; female:male = 38.5%:61.5%
   b. Median (range) duration of pain (months) 64 (12 to 180)
   c. Major pain site (%) upper limb = 53.8, lower limb = 23.1, both = 23.1

Inclusion criteria:

1. Diagnosis of CRPS I or II

Exclusion criteria: not reported

Interventions	**VBS (n = 13)** Components of intervention: in a semi-reclined position and wearing a VR 2000 3D Visor Head-Mounted Display (HMD) (League City, Texas, USA), participants watched a video clip consisting of 4 actions ('making the fists and opening up the fingers', 'bending and unbending the elbows', 'bending the ankles forward and backward', and 'bending and unbending the legs'). Participants were asked to mentally synchronise their own movements with the movements displayed on the HMD. Dosage: participants watched the video clip twice with a 1-minute break between sessions (not exceeding 10 minutes) Frequency of administration: single session Provider: not reported **WM (n = 13)** Components of intervention: in a semi-reclined position and wearing a VR 2000 3D Visor Head-Mounted Display (HMD) (League City, Texas, USA), participants watched a video clip consisting of 4 actions ('making the fists and opening up the fingers', 'bending and unbending the elbows', 'bending the ankles forward and backward', and 'bending and unbending the legs'). Participants were asked to simply watch the video clip on the HMD, which was the same video used in the VBS group. Dosage: participants watched the video clip twice with a 1-minute break between sessions (not exceeding 10 minutes) Frequency of administration: single session Provider: not reported **MR (n =13)** Components of intervention: in a semi-reclined position participants listened to a voice recording consisting of 4 imaginary actions: 'making the fists and opening up the fingers', 'bending and unbending the elbows', 'bending the ankles forward and backward', and 'bending and unbending the legs'. Dosage: participants listened to the voice recording twice with a 1-minute break between sessions (not exceeding 10 minutes) Frequency of administration: single session Provider: not reported
Outcomes	Outcomes assessed at baseline and on completion of the intervention period

Hwang 2014 *(Continued)*

1. Self-reported pain intensity assessed using an 11-point Likert scale (0 = not at all; 10 = very uncomfortable)
2. Self-reported body perception disturbance assessed using the modified 9-item Body Perception Disturbance Questionnaire (score range 0 to 90, with higher score indicating greater body perception disturbance)

Notes	**Source of funding:** the trial was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (2012R1A1A2008624) **Statement regarding declarations of interest:** the authors declared no conflicts of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "All participants were assigned randomly to one of the three experimental groups". Comment: the trial authors did not report the method of sequence generation.
Allocation concealment (selection bias)	Unclear risk	Comment: the trial authors did not report the method of allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: given the nature of the intervention, participants were not blinded to treatment allocation but the extent to which the lack of blinding may have introduced bias is uncertain. Comment: the trial authors did not give a statement of procedures regarding blinding of personnel and the extent to which the lack of blinding may have introduced bias is uncertain.
Blinding of outcome assessment (detection bias) Self-reported outcomes	Unclear risk	Comment: given the nature of the intervention, participants were not blinded to treatment allocation but the extent to which the lack of blinding may have introduced bias is uncertain.
Blinding of outcome assessment (detection bias) Investigator-administered outcomes	Low risk	Not applicable.
Incomplete outcome data (attrition bias) Dropout rate described and acceptable	Unclear risk	Comment: the trial authors did not explicitly report the dropout rate.
Incomplete outcome data (attrition bias) Participants analysed in the group to which they were allocated	Unclear risk	Comment: the method of analysis (ITT versus per protocol) was not reported.
Selective reporting (reporting bias)	High risk	Comment: the trial authors did not fully report outcome data for all outcomes reported in the methods section of the publication.
Sample size	High risk	Quote: "The participants were 39 patients with CRPS". Comment: the small sample size may have introduced bias in the estimates of treatment effect.

Hwang 2014 *(Continued)*

Duration of follow-up	High risk	Quote: "Pretreatment pain intensity and BPD were compared with post-treatment perceptions". Comment: the trial authors re-evaluated participants at the end of the treatment period only.
Other bias	Unclear risk	Comment: some baseline imbalances between groups with respect to gender and duration of pain.

Jeon 2014

Study characteristics	
Methods	**Design:** parallel-group, 2-arm, placebo-controlled pilot RCT **Setting:** tertiary university pain centre (South Korea; dates not reported) **Interventions:** virtual body swapping with mental rehearsal or virtual body swapping alone **Sample size calculation:** pilot RCT with bootstrapping method to increase the robustness of small-sample analyses
Participants	**Number of participants:** 10 (number per group not reported) **Type of noxious initiating event:** not reported (upper limb only n = 1, lower limb only n = 1, multiple limbs n = 4, and whole body n = 4) **Diagnostic criteria:** Harden 2007 (CRPS I) **Baseline characteristics:** Total sample (separate intervention and control group data not reported but no statistically significant between-group differences) Mean (SD) age: 39.30 (10.99) years; female:male = 0:10 Median (range) duration of CRPS I: 52 (33 to 120) months **Inclusion criteria:** CRPS I **Exclusion criteria:** not reported
Interventions	The trial authors did not report any co-interventions. **Virtual body swapping with mental rehearsal (n = not reported)** Components of intervention: 1. Whilst lying down and wearing a head mounted display (VR2000; Virtual Realities, Ltd.) participants watched a virtual body swapping training video in order to evoke a virtual body swapping illusion. The 3 minute 20 second long video clip was filmed from the first person perspective and consisted of 4 physical movements (making fists and opening up the fingers, bending and unbending the elbows, bending the ankles forward and backward, and bending and unbending the legs). The first person perspective would help participants to feel as if they observed their body when they watch the video. 2. Participants were additionally asked to assume a posture similar to that of the body on the screen and rehearse the movements mentally, as if the body presented on the display was their own body. Dosage: 1 training session Frequency of administration: the experimental video clip was played twice with a 1-minute break given between viewings

Jeon 2014 *(Continued)*

	Provider: 1 specialist in pain and 2 assistants (trained graduate students); professional discipline not reported **Virtual body swapping alone (n = not reported)** Components of intervention: participants watched the same video but did not perform mental rehearsal of the 4 physical movements Dosage: 1 training session Frequency of administration: the experimental video clip was played twice with a 1-minute break given between viewings Provider: 1 specialist in pain and 2 assistants (trained graduate students); professional discipline not reported
Outcomes	The trial authors did not explicitly specify the time points at which they measured outcomes in the trial report. The outcomes were assessed immediately pre-intervention and postintervention. The trial authors did not state any primary outcome. 1. Self-rated pain intensity measured on an 11-point Likert scale ranging from 0 (no pain) to 10 (severe pain) 2. The modified Body Perception Disturbance Questionnaire (BPDQ) consisting of 9 items with each item rated on an 11-point scale ranging from 0 (not at all) to 10 (very likely). Scores range from 0 to 90 with higher scores indicating greater body perception disturbance.
Notes	**Source of funding:** Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (2012R1A1A2008624) and the Chung-Ang University Excellent Student Scholarship in 2014 **Statement regarding declarations of interest:** none declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Ten patients who met the diagnostic criterion for CRPS type 1 were randomly assigned to either the treatment or control group". Comment: the trial authors did not report the method of sequence generation.
Allocation concealment (selection bias)	Unclear risk	Comment: the trial authors did not report the method of allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: given the nature of the intervention, participants were not blinded to treatment allocation but the extent to which the lack of blinding may have introduced bias is uncertain.
Blinding of outcome assessment (detection bias) Self-reported outcomes	Unclear risk	Comment: given the nature of the intervention, participants were not blinded to treatment allocation but the extent to which the lack of blinding may have introduced bias is uncertain.
Blinding of outcome assessment (detection bias) Investigator-administered outcomes	Low risk	Not applicable.
Incomplete outcome data (attrition bias)	Low risk	Comment: the trial authors did not report the dropout rate but, given the intervention comprised a single session with post-intervention follow-up only it is likely there were no dropouts.

Jeon 2014 *(Continued)*

Dropout rate described and acceptable		
Incomplete outcome data (attrition bias) Participants analysed in the group to which they were allocated	Low risk	Comment: the trial authors did not report the method of analysis but, given the methodology, it is likely that they analysed all participants in the group to which they were allocated.
Selective reporting (reporting bias)	High risk	Quote: "There was no significant difference between the groups in pain intensity, F(1, 7) = 0.05, p = 0.81". Comment: the trial authors did not report any pre-intervention or postintervention outcome data for self-reported pain intensity.
Sample size	High risk	"Ten patients with CRPS type 1 were recruited from a tertiary university pain center in Seoul, Korea". Comment: the small sample size may have introduced bias in the estimates of treatment effect.
Duration of follow-up	High risk	Quote: "The experimental video clip was played twice with a 1-minute break given between viewing's. The participants were then asked to respond to the pain intensity question...and to complete the BPDQ". Comment: the trial authors re-measured outcomes on immediate completion of the intervention period only and did not measure them over a clinically relevant length of time.
Other bias	Unclear risk	Comment: the trial authors did not report baseline pain data.

Lewis 2021

Study characteristics	
Methods	**Design:** parallel, 2-arm RCT **Setting:** clinics a the Royal National Hospital for Rheumatic Diseases, Royal United Hospitals Bath NHS Foundation Trust, Bath and The Walton Centre NHS Foundation Trust, Liverpool (United Kingdom, dates not reported) **Interventions:** mediated virtual reality or sham mediated virtual reality **Sample size calculation:** a total sample size of 88 participants (44 per group) was calculated as sufficient for a mean (SD) reduction on the 11-point numerical pain rating scale of 1.733 (2.89) points, with 80% power and a 0.05 two-sided significance
Participants	**Number of participants:** 45 (experimental group n = 23; control group n = 22) **Type of noxious initiating event:** not reported (upper limb) **Diagnostic criteria:** 'Budapest criteria' Harden 2010 (CRPS type not reported) **Baseline characteristics:** 1. Mediated virtual reality: a. Mean (SD) age = 52 (11) years; female:male = 15:8 b. Mean (SD) duration of CRPS I: 49 (51) months 2. Sham mediated virtual reality:

Lewis 2021 *(Continued)*

a. Mean (SD) age = 52 (14.5) years; female:male = 14:8
b. Mean (SD) duration of CRPS I: 63 (56) months

Inclusion criteria:

1. Meet the Budapest criteria for CRPS in one upper limb
2. ≥ 18 years of age
3. Describes an altered perception of their painful body
4. Able to understand verbal and written English
5. Willing to participate and provide written informed consent

Exclusion criteria:

1. Serious ill health
2. Bilateral upper limb involvement
3. Dystonia
4. Co-morbidity that may influence CRPS symptoms
5. Currently participating in an intervention trial

Interventions	**Mediated virtual reality (n = 23)** Components of intervention: 1. Participants sat with each arm placed into one of the two apertures of the MIRAGE system with hands rested palm down within the system. Participants viewed a real-time digital video of their hands through a horizontal 'window-like' surface above and perpendicular to the apertures. The image of their hands was displayed via this surface so the hand image appeared to be in the same location as their actual hands. 2. The MIRAGE system operator digitally altered the appearance of the painful hand using specifically designed software via a laptop (MacBook Pro 15" Model ME664B/A using Windows 7 running LabView 2012 (National Instruments)). Real-time changes to aspects of shape, size and/or colour of the hand based on the participant's desired hand appearance were made. Images were altered based on participant reports of hand appearance satisfaction; if participants rated their satisfaction <+1 on a 7-point Likert scale, the image was altered to reach a rating of +1. Requests were specific to each individual and took up to a minute to complete. Once participants were satisfied, they viewed the resultant image for one minute. No visual changes were made to the unaffected hand. Dosage: up to 5 sessions of 30 minutes duration each Frequency of administration: not reported Provider: not reported **Sham mediated virtual reality (n = 22)** Components of the intervention: the procedure and duration were identical to the experimental group with the exception that the image of the participant's hand was not visually altered, though the participant believed it to have been. A satisfaction rating of <+1 was not required to proceed with the intervention. Dosage: up to 5 sessions of 30 minutes duration each Frequency of administration: not reported Provider: not reported
Outcomes	Outcomes were assessed pre-intervention and post-intervention, and a subgroup was followed up 2 weeks post-intervention. **Primary outcomes:**

Lewis 2021 *(Continued)*

	1. Body perception of the affected limb using the Bath Body Perception Disturbance (BPD) scale, with higher scores indicating a greater degree of disturbance (score range not reported) 2. Self-rated current pain using an 11-point Numerical Rating Scale (NRS), anchored with 0 "no pain" and 10 "worst pain imaginable" 3. Subjective perceptual changes associated with the affected hand by providing perceptual statement ratings to two statements on a 7-point Likert scale ranging from -3 "strongly disagree" to + 3 "strongly agree" **Secondary outcomes:** 1. Self-reported severity of neuropathic pain using the Neuropathic Pain Symptom Inventory (NPSI), different neuropathic symptoms are rated on an 11-point numerical rating scale and a total score is created by summing the 5 categories; higher scores denote greater intensity (score range not reported)
Notes	**Source of funding:** one researcher's salary and the costs of the project were funded by a National Institute for Health Research Post-Doctoral Fellowship (grant number CAT-CL-03-2012-019) **Statement regarding declarations of interest:** no conflicts of interests were declared for any author

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "a person independent of data collection used a computer generated random sequence to produce information regarding group allocation". Comment: the trial authors used an acceptable method to generate the allocation sequence.
Allocation concealment (selection bias)	Low risk	Quote: "in advance of testing, a person independent of data collection used a computer generated random sequence to produce information regarding group allocation that was placed in sealed and numbered envelopes". Comment: the trial authors used an acceptable method to conceal the allocation sequence.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "to minimise performance and detection bias, the clinical assessor and participants were blinded to group allocation. Participants were not informed of the study hypothesis to minimise responder bias". Comment: the participants were blinded to treatment allocation. Comment: care provider not blinded but we judge that both intervention arms reflect active interventions of relatively equal credibility delivered with equal enthusiasm such that outcomes were unlikely to be influenced by a lack of blinding.
Blinding of outcome assessment (detection bias) Self-reported outcomes	Low risk	Quote: "to minimise performance and detection bias, the clinical assessor and participants were blinded to group allocation. Participants were not informed of the study hypothesis to minimise responder bias." Comment: the participants who completed self-reported outcome measures were blinded to treatment allocation.
Blinding of outcome assessment (detection bias) Investigator-administered outcomes	Low risk	Quote: "the clinical assessor and participants were blinded to group allocation" Comment: outcome assessors were blinded to participants group allocation.

Lewis 2021 *(Continued)*

Incomplete outcome data (attrition bias) Dropout rate described and acceptable	Unclear risk	Quote: "Analysis of data was conducted in 45 participants for single exposure and in 39 participants for repeated exposure and follow up". Comment: there were no dropouts for the primary outcome but there was an unequal dropout rate between groups at follow-up (E = 9%, C = 18%). Reasons for dropout were given.
Incomplete outcome data (attrition bias) Participants analysed in the group to which they were allocated	Unclear risk	Comment: the authors did not provide a statement detailing whether the participants were analysed in the group to which they were randomised.
Selective reporting (reporting bias)	High risk	Comment: the trial authors fully reported outcome data graphically for all outcomes; but did not report raw data in numerical form with measures of variation.
Sample size	High risk	Quote: "Forty-five participants were randomised". Comment: the small sample size may have introduced bias in the estimates of treatment effect.
Duration of follow-up	High risk	Quote: "BPD and pain were measured pre and post-intervention". Comment: the trial authors did not measure outcomes over a clinically relevant length of time.
Other bias	Low risk	Comment: we did not identify any other sources of bias.

Li 2012

Study characteristics	
Methods	**Design:** parallel-group, 2-arm RCT **Setting:** hospital (China; July 2008 to July 2010) **Interventions:** acupuncture and massage or rehabilitation therapy **Sample size calculation:** not reported
Participants	**Number of participants:** 120 (60 per group) **Type of noxious initiating event:** stroke (upper limb) **Diagnostic criteria:** Steinbrocker 1948 (stage 1) **Baseline characteristics:** 1. Acupuncture and massage: a. Mean (±) age = 62 (12) years; female:male = 20:40 b. Mean (±) duration of shoulder-hand syndrome = 28 (6) days 2. Rehabilitation: a. Mean (±) age = 61 (13) years; female:male = 19:41 b. Mean (±) duration of shoulder-hand syndrome 27 (5) days **Inclusion criteria:** 1. Ischaemic stroke

Li 2012 *(Continued)*

2. Age 18 to 75 years
3. Clinical symptoms of shoulder-hand syndrome conforming to stage I of the Steinbrocker criteria
4. Fixed address and agreement to long-term follow-up visits
5. Sufficient cognitive ability to consent

Exclusion criteria:

1. Shoulder-hand syndrome caused by a second stroke, cerebral haemorrhage, cerebral tumour or trauma
2. Shoulder-hand syndrome at stage II or III
3. Pain or restricted shoulder motion secondary to dislocation or subluxation, fracture or brachial plexus injury
4. Severe heart, liver or kidney disease
5. Severe cognitive dysfunction, mental disorder, malnutrition or poor general condition
6. Unable to consent

Interventions	**Acupuncture and massage (n = 60)** Components of intervention: 1. Acupuncture: electric and non-electric acupuncture involving the following points: Sanjian (LI 3), Houxi (SI 3), Zhongzhu (SJ 3), Jianzhongshu (SI 15), Jianliao (SJ 14), Shousanli (LI 10), Waiguan (SJ 5) and Tianzong (SI 11) 2. Massage: massage of the affected upper limb, passive shoulder movements without pain Dosage: acupuncture = 25 minutes, massage = 25 minutes Frequency of administration: once per day for 6 therapeutic courses; each course comprised 5 sessions, with a 2-day interval between courses (30 sessions) Provider: doctors **Rehabilitation therapy (n = 60)** Components of intervention: active-assisted scapular movements; Bobath exercises to clench the fist, functional transfers (e.g. changing position from prone to sitting, sitting to standing); proprioceptive neuromuscular facilitation (PNF) Dosage: active-assisted scapular movements = 15 minutes, Bobath exercises and functional transfers = 15 minutes, PNF = 10 minutes Frequency of administration: once per day for 6 therapeutic courses; each course comprised 5 sessions, with a 2-day interval between courses (30 sessions) Provider: doctors
Outcomes	The trial authors assessed outcomes at baseline, at the end of the 6-week treatment period and at 12 weeks post-treatment **Primary outcomes:** 1. Self-rated pain on passive shoulder motion (direction of motion not described) to 90° with the participant in a seated position using a numeric pain rating scale (scale characteristics not reported) 2. Number of participants with shoulder-hand syndrome at Steinbrocker stage II or III after treatment **Secondary outcomes** 1. Fugl-Meyer evaluation of functional movement of the upper limb (33 items, maximum possible score = 66; higher scores indicating more normal movement) 2. Fugl-Meyer evaluation of functional movement of the hand (7 items, maximum possible score = 14; higher scores indicating more normal movement) 3. Modified Rankin scale (scale properties and scoring method not reported)

Li 2012 *(Continued)*

	4. Adverse events (incidence of shoulder dislocation, fainting during acupuncture, haematoma, other)
Notes	**Source of funding:** not reported **Statement regarding declarations of interest:** not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A random encoding plan was designed using SPSS software". Comment: the trial authors used an acceptable method to generate the allocation sequence.
Allocation concealment (selection bias)	Low risk	Quote: "A random encoding plan was designed using SPSS software and concealed in an envelope Comment: the trial authors used an adequate method to conceal the allocation sequence.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: given the nature of the intervention, participants were not blinded to treatment and may have had different expectations about the benefits of each intervention.
Blinding of outcome assessment (detection bias) Self-reported outcomes	High risk	Comment: unblinded participants who may have had different expectations about the benefits of the intervention they received self-reported some outcomes (e.g. pain intensity).
Blinding of outcome assessment (detection bias) Investigator-administered outcomes	Unclear risk	Comment: the trial authors did not give a statement of procedures regarding blinding of the outcome assessor.
Incomplete outcome data (attrition bias) Dropout rate described and acceptable	Low risk	Quote: "All patients finished the treatment and had a follow-up visit". Comment: all randomly assigned participants completed the study.
Incomplete outcome data (attrition bias) Participants analysed in the group to which they were allocated	Low risk	Quote: "All patients finished the treatment and had a follow-up visit". Comment: the trial authors did not report the method of analysis (ITT versus per protocol).
Selective reporting (reporting bias)	Low risk	Comment: the trial authors fully reported outcome data for all outcomes reported in the methods section of the publication.
Sample size	Unclear risk	Quote: "The 120 subjects in this series...were selected from 202 stroke patients...They were randomly divided into an acupuncture-massage group and a rehabilitation group, with 60 cases in each". Comment: the extent to which the small to moderate sample size may have introduced bias into estimates of treatment effect is uncertain.
Duration of follow-up	Low risk	Quote: "Each of the above indices was recorded before treatment, at the end of the 6-week treatment period and at the 12th-week follow-up visit".

Li 2012 *(Continued)*

		Comment: the trial authors measured outcomes over a clinically relevant length of time.
Other bias	Low risk	Comment: we did not identify any other sources of bias.

Moseley 2004

Study characteristics

Methods	**Design:** single-blind, 2-arm RCT. (The trial author reported that participants in the control group crossed over into the experimental group. However, we deemed that this trial had not employed a true cross-over design and we analysed it as a 2-arm parallel-group trial up to the endpoint just prior to cross-over). **Setting:** hospital physiotherapy department (Australia; dates not reported) **Interventions:** graded motor imagery (GMI) or ongoing medical management **Sample size calculation:** not reported
Participants	**Number of participants:** 13 (experimental group n = 7; control group n = 6) **Type of noxious initiating event:** wrist fracture (upper limb) **Diagnostic criteria:** Bruehl 1999 (CRPS I) **Baseline characteristics:** 1. GMI: a. Mean (SD) age = 35 (15) years; female:male = 5:2 b. Mean (SD) duration of CRPS I: 51 (18) weeks 2. Ongoing medical management: a. Mean (SD) age = 38 (14) years; female:male = 4:2 b. Mean (SD) duration of CRPS I: 65 (19) weeks **Inclusion criteria:** > 6 months post non-complicated wrist fracture **Exclusion criteria:** 1. Previously benefited from an intravenous regional sympathetic blockade 2. Any other upper limb pathology or pain 3. Any neurological or motor disorder including dyslexia or difficulty performing a rapid naming task 4. Visually impaired 5. A diagnosed psychopathology 6. Any invasive analgesic strategy (e.g. spinal cord stimulator) 7. Lived beyond the immediate metropolitan area of the host department
Interventions	**GMI (n = 7)** Components of intervention: 1. Recognition of hand laterality stage (2 weeks): whilst seated at a computer monitor, participants viewed a random sequence of 56 photographic images of either a right or left hand in a variety of postures. Participants were instructed to identify whether the displayed image was of a right or left hand by pressing an appropriate button on the computer keyboard. participants borrowed a note-book computer to repeat the task at home.

Moseley 2004 *(Continued)*

2. Imagined hand movements stage (2 weeks): whilst viewing a random sequence of 28 images of the affected hand participants were advised to deliberately imagine moving their hand to adopt the posture shown in the picture, 3 times
3. Mirror therapy stage (2 weeks): using a mirror box which concealed the affected limb from view but allowed participants to view a mirror image of their unaffected limb, participants viewed a sequence of 20 pictures of the unaffected hand and were instructed to slowly and smoothly adopt the posture shown in each picture with both hands. Emphasis was placed on watching the reflection of their unaffected hand in the mirror.

Dosage: hand laterality and imagined movements tasks - 3 times; mirror therapy task - 10 times

Frequency of administration: each waking hour, daily for 2 weeks (6 weeks in total)

Provider: not reported

Ongoing medical management (n = 6)

Components of intervention:

1. No limitations placed on treatment
2. Participants were requested not to change medication type or dosage and to record any new treatments received
3. Predominantly physical therapy (2 to 3 sessions per week) comprising active and passive limb mobilisation, systemic desensitisation and hydrotherapy
4. Chiropractic manipulation and acupuncture (1 participant); psychological counselling (1 participant)

Outcomes	Trial authors assessed outcomes at baseline, at 2 and 4 weeks after commencement of treatment, at the end of the 6-week treatment period (week 6) and 6 weeks post-treatment (week 12). The trial authors did not state a primary outcome. 1. Neuropathic pain scale (NPS), with responses regarding the 2 previous days (scoring properties not reported) 2. Swelling, using the average of measure of the circumference of the base of the 2nd and 3rd digits, as measured with a hand measuring tape
Notes	**Source of funding:** Clinical Research Fellowship from the National Health and Medical Research Council of Australia ID 210348 **Statement regarding declarations of interest:** not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomised by an independent investigator to the 6-week MIP treatment group or to ongoing medical management (control) using a random number table". Comment: the trial authors used an acceptable method to generate the allocation sequence.
Allocation concealment (selection bias)	Unclear risk	Comment: the trial authors did not report the method of allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: given the nature of the intervention, participants were not blinded to treatment and may have had different expectations about the benefits of each intervention.

Moseley 2004 *(Continued)*

Blinding of outcome assessment (detection bias) Self-reported outcomes	High risk	Comment: unblinded participants, who may have had different expectations about the benefits of the intervention they received, self-reported some outcomes (e.g. NPS).
Blinding of outcome assessment (detection bias) Investigator-administered outcomes	Low risk	Quote: "All assessments were made by a separate investigator who was blind to experimental group and measurement occasion". Comment: the outcome assessor of objective outcomes was blinded to treatment allocation.
Incomplete outcome data (attrition bias) Dropout rate described and acceptable	Low risk	Comment: all randomly assigned participants completed the study (as displayed in the published report's 'Experimental plan').
Incomplete outcome data (attrition bias) Participants analysed in the group to which they were allocated	Low risk	Comment: the trial authors analysed participants in the group to which they were allocated.
Selective reporting (reporting bias)	High risk	Comment: the trial authors fully reported outcome data graphically for all outcomes, but did not report raw data in numerical form with measures of variation.
Sample size	High risk	Quote: "Written informed consent was obtained from the remaining 13 subjects". Comment: the small sample size may have introduced bias in the estimates of treatment effect.
Duration of follow-up	Unclear risk	Quote: "Post hoc analyses showed...a significant reduction in all three variables during the MIP with the effect maintained for at least 6 weeks after the completion of treatment". Comment: the clinical relevance of a 6-week follow-up of outcomes is uncertain.
Other bias	Unclear risk	Comment: we did not identify any other sources of bias.

Moseley 2005

Study characteristics	
Methods	**Design:** parallel-group, 3-arm, single-blind RCT **Setting:** not reported (Australia; dates not reported) **Interventions:** hand laterality recognition followed by imagined movements followed by mirror movements (RecImMir, MIP) or imagined movements followed by laterality recognition followed by imagined movements (ImRecIm) or laterality recognition followed by mirror movements followed by recognition (RecMirRec) **Sample size calculation:** not reported
Participants	**Number of participants:** 20 (RecImMir, MIP group (1) n = 7; ImRecIm group (2) n = 6; RecMirRec group (3) n = 7)

Moseley 2005 *(Continued)*

Type of noxious initiating event: wrist fracture (upper limb)

Diagnostic criteria: Bruehl 1999 (CRPS I)

Baseline characteristics:

1. RecImMir, MIP:
   a. Mean (SD) age = 36 (8) years; female:male = 5:2
   b. Mean (SD) duration of CRPS I: 12 (6) months
2. ImRecIm:
   a. Mean (SD) age = 27 (7) years; female:male = 4:2
   b. Mean (SD) duration of CRPS I: 16 (5) months
3. RecMirRec:
   a. Mean (SD) age = 39 (8) years; female:male = 5:2
   b. Mean (SD) duration of CRPS I: 14 (5) months

Inclusion criteria: onset of CRPS I post non-complicated wrist fracture > 6 months prior to enrolment

Exclusion criteria:

1. Previously obtained relief from an intravenous regional sympathetic blockade
2. Any invasive analgesic strategy (e.g. spinal cord stimulator, sympathectomy)
3. Any other neurological, psychopathology or motor disorder or dyslexia
4. Difficulty performing a rapid naming task
5. Visually impaired
6. Any other upper limb pathology or pain
7. Lived outside the immediate metropolitan area of the host department

Interventions

Participants were advised to avoid changing medication or seeking alternative treatment during the course of the trial up to and including the 12-week follow-up. Participants were permitted to attend physiotherapy during the 12-week follow-up, but no criteria about physiotherapy were set.

RecImMir, group 1 (n = 7)

Components of intervention:

1. Hand laterality recognition (2 weeks): whilst seated at a computer monitor, participants viewed a random sequence of 56 photographic images of either a right or left hand in a variety of postures. Participants were instructed to identify whether the displayed image was of a right or left hand by pressing an appropriate button on the computer keyboard. Participants borrowed a notebook computer to repeat the task at home.
2. Imagined hand movements (2 weeks): whilst viewing a random sequence of 28 images of the affected hand participants were advised to imagine moving their own hand to adopt the posture shown in the picture then returning it to its resting position, and to repeat the process twice for each picture.
3. Mirror therapy (2 weeks): using a mirror box which concealed the affected limb from view but allowed participants to view a mirror image of their unaffected limb, participants viewed a sequence of 20 pictures of the unaffected hand and were instructed to slowly and smoothly adopt the posture shown in each picture with both hands. Emphasis was placed on watching the reflection of their unaffected hand in the mirror.

Dosage: hand laterality task - 3 times, imagined movements task - twice; mirror therapy task - 5 times

Frequency of administration: each waking hour, daily for 2 weeks (6 weeks in total)

Provider: not reported

ImRecIm, group 2 (n = 6)

Components of intervention: 2 weeks imagined movements, 2 weeks hand laterality recognition, 2 weeks imagined movements (components described above)

Moseley 2005 *(Continued)*

	Dosage and frequency of administration: as described above **RecMirRec, group 3 (n = 7)** Components of intervention: 2 weeks hand laterality recognition, 2 weeks mirror therapy, 2 weeks hand laterality recognition (components described above) Dosage and frequency of administration: as described above
Outcomes	The trial authors assessed outcomes at baseline, at 2 and 4 weeks after commencement of treatment, at the end of the 6-week treatment period (week 6) and 12 weeks post-treatment (week 18). The trial authors did not state a primary outcome. 1. NPS, with responses regarding the 2 previous days (possible range 0 to 100) 2. Self-rated function with respect to 5 self-selected activities or tasks using an 11-point numerical rating scale (NRS) anchored with "0, completely unable to perform" and "10, able to perform normally" (final score average of 5 tasks, possible range 0 to 10 higher number indicates less severe limitation)
Notes	**Source of funding:** Australian Clinical Research Fellowship from the National Health and Medical Research Council of Australia ID 210348 **Statement regarding declarations of interest:** not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Using a random numbers table, an independent investigator allocated consenting patients into one of three treatment groups". Comment: the trial authors used an acceptable method to generate the allocation sequence.
Allocation concealment (selection bias)	Unclear risk	Comment: the trial authors did not report the method of allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: participants were not blinded to treatment allocation but a lack of blinding is unlikely to have biased the results given that participants received interventions judged to have been of relatively equal credibility.
Blinding of outcome assessment (detection bias) Self-reported outcomes	Low risk	Comment: participants were not blinded to treatment allocation and self-reported their outcomes but lack of blinding unlikely to have biased the results given that participants received interventions judged to have been of relatively equal credibility.
Blinding of outcome assessment (detection bias) Investigator-administered outcomes	Unclear risk	Not applicable.
Incomplete outcome data (attrition bias) Dropout rate described and acceptable	Low risk	Comment: all but one randomly assigned participant completed the study, and the one participant appeared to have dropped out from group 3 (as displayed in the published report's 'Treatment plan').
Incomplete outcome data (attrition bias)	High risk	Comment: the trial authors did not report the method of analysis (ITT versus per protocol). The trial authors appear to have excluded one participant from group 3 from the analysis in an apparent violation of the principle of ITT.

Moseley 2005 *(Continued)*

Participants analysed in the group to which they were allocated		
Selective reporting (reporting bias)	High risk	Comment: the trial authors fully reported outcome data graphically for all outcomes; but did not report raw data in numerical form with measures of variation.
Sample size	High risk	Quote: "Twenty subjects with chronic CRPS1 initiated by wrist fracture and who satisfied stringent inclusion criteria, were randomly allocated to one of three groups". Comment: the small sample size may have introduced bias in the estimates of treatment effect.
Duration of follow-up	Low risk	Quote: "Single blind randomised trial with 12-week follow-up". Comment: the trial authors measured outcomes over a clinically relevant length of time.
Other bias	Unclear risk	Comment: we did not identify any other sources of bias.

Moseley 2006

Study characteristics	
Methods	**Design:** parallel-group, 2-arm, single-blind RCT. NB: this trial recruited participants with CRPS I and phantom limb pain. However, we only included information and data from participants with CRPS for the purpose of this systematic review. **Setting:** not reported (Australia; dates not reported) **Interventions:** GMI or physiotherapy and ongoing medical care **Sample size calculation:** a total sample size of 51 participants would detect an effect size of 0.80 (equivalent to a reduction in pain of 29 mm on a 100 mm VAS), with a probability of 80%, assuming an alpha level of 0.05
Participants	**Number of participants:** 37 (experimental group n = 17; control group n = 20) **Type of noxious initiating event:** mixed (fractures n = 14, soft-tissue injury n = 15, post carpal tunnel release n = 2, venepuncture site n = 2, post finger/toe amputation n = 2, carpal tunnel syndrome n = 1, nail infection n = 1) (upper and lower limb) **Diagnostic criteria:** Bruehl 1999 (CRPS I) **Baseline characteristics:** 1. GMI: a. Mean (SD) age = 45 (14) years; female:male = 11:6 b. Mean (SD) duration of CRPS I: 14 (10) months 2. Physical therapy and ongoing medical care: a. Mean (SD) age = 41 (14) years; female:male = 15:5 b. Mean (SD) duration of CRPS I: 12 (8) months **Inclusion criteria:** CRPS I of an upper or lower limb **Exclusion criteria:**

Moseley 2006 *(Continued)*

1. Any other neurologic, psychopathology or motor disorder
2. Dyslexia
3. Difficulty performing a rapid naming task
4. Visually impaired
5. Any other limb pathology or pain
6. Lived outside the immediate metropolitan area of the host department

Interventions	**GMI (n = 17)** Components of intervention: 1. Limb laterality recognition phase (2 weeks): whilst seated at a computer, participants viewed a random sequence of photographic images (matched to gender) of either a right or left hand (participants with an affected upper limb) or foot (participants with an affected lower limb) in a variety of positions and alignments. Participants indicated whether the displayed image was of a right or left limb by pressing an appropriate key on the computer keyboard; 2. Imagined movements phase (2 weeks): whilst viewing a random sequence of images of both limbs participants were required to imagine twice adopting the posture shown with a smooth and pain-free movement; 3. Mirror movements phase (2 weeks): using a mirror box which concealed the affected limb from view but allowed participants to view a mirror image of their unaffected limb, participants viewed a sequence of images and were instructed to twice adopt the posture shown with both limbs, using smooth and pain-free movements. Dosage: participants were prescribed a training protocol of gradually increased training load according to task difficulty during each of the 3 GMI phases, as detailed by the trial authors Frequency of administration: hourly training (further details not reported) Provider: physiotherapist **Physiotherapy and ongoing medical care (n = 20)** Components of intervention: not reported Dosage: not reported Frequency of administration: minimum of once per week together with an hourly home programme Provider: physiotherapists
Outcomes	Outcomes assessed at baseline, at the end of the 6-week treatment period and 6 months post-treatment **Primary outcomes:** 1. Self-rated function with respect to 5 self-selected activities or tasks using an 11-point NRS anchored with "0, completely unable to perform" and "10, able to perform normally" 2. Self-rated pain severity using a 0 to 100 mm VAS (anchor points not described) to rate average level of pain over the last 2 days 3. McGill Pain Questionnaire (MPQ)
Notes	Original trial publication reported data for participants with CRPS I and phantom limb pain (N = 51). Details reported above refer to only those participants with CRPS I (N = 37). **Source of funding:** not reported **Statement regarding declarations of interest:** the authors declared no conflicts of interest
Risk of bias	

Moseley 2006 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomized via random number generation by an independent investigator...using a random numbers table". Comment: the trial authors used an acceptable method to generate the allocation sequence.
Allocation concealment (selection bias)	Unclear risk	Comment: the trial authors did not report the method of allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: given the nature of the intervention, participants were not blinded to treatment and may have had different expectations about the benefits of each intervention.
Blinding of outcome assessment (detection bias) Self-reported outcomes	High risk	Comment: unblinded participants, who may have had different expectations about the benefits of the intervention they received, self-reported some outcomes (e.g. pain intensity).
Blinding of outcome assessment (detection bias) Investigator-administered outcomes	Low risk	Not applicable.
Incomplete outcome data (attrition bias) Dropout rate described and acceptable	Low risk	Quote: "One female subject in the control group withdrew from the study because she sustained an unrelated injury. There were no other dropouts or withdrawals". Comment: the minimal dropout rate (5% from 1 trial arm) is unlikely to have biased the results.
Incomplete outcome data (attrition bias) Participants analysed in the group to which they were allocated	Low risk	Comment: the trial authors performed an available case analysis and there was only 1 loss to follow-up.
Selective reporting (reporting bias)	Low risk	Comment: the trial authors fully reported outcome data for self-reported function and pain severity outcomes for participants with CRPS and phantom limb pain combined as conceived in the original trial design. They presented outcome data for participants with CRPS graphically only.
Sample size	High risk	Quote: "Fifty-one patients [37 with CRPS] with phantom limb pain or CRPS1 were randomly allocated". Comment: the small sample size may have introduced bias in the estimates of treatment effect. (We acknowledge that our judgement regarding the risk of bias linked to sample size for this study is based on the purposeful exclusion of a number of participants with phantom limb pain (N = 14) that the original design did not intend).
Duration of follow-up	Low risk	Quote: "All assessments were undertaken at prerandomization and at 6 weeks (completion of the treatment period). Pain VAS and function NRS were also undertaken at 6 months follow-up". Comment: the trial authors measured outcomes over a clinically relevant length of time.

Moseley 2006 *(Continued)*

Other bias	Unclear risk	Comment: we did not identify any other sources of bias.

Moseley 2009

Study characteristics	
Methods	**Design:** within-subject randomised cross-over design **Setting:** not reported (Australia; dates not reported) **Interventions:** tactile discrimination training (TDT) under 4 separate conditions **Sample size calculation:** not reported
Participants	**Number of participants:** 10 **Type of noxious initiating event:** mixed (fractures of the hand or wrist n = 4, sprains n = 2, carpal tunnel syndrome n = 2, post hand cannulation n = 1, thumb dislocation n = 1) (upper limb) **Diagnostic criteria:** Bruehl 1999 (CRPS I) **Baseline characteristics:** 1. Mean (SD) age = 43 (11) years; female:male = 6:4 2. Mean (SD) duration of CRPS I: 20 (5) months **Inclusion criteria:** CRPS of 1 wrist of hand **Exclusion criteria:** not reported
Interventions	**TDT (n = 10)** Components of intervention: 1. 2 probes (2 mm and 12 mm in diameter) were applied to 1 of 5 stimulation sites on the affected limb in a random order, with an interstimulus interval of 15 seconds 2. TDT was performed under 4 different conditions: a. Facing + skin: involved participants watching the reflected image of their unaffected, non-stimulated arm in a mirror placed between the upper limbs while facing the stimulated arm b. Skin only: involved participants watching their unaffected, non-stimulated arm directly c. Facing only: involved participants looking in the direction of their affected, stimulated arm but with no mirror and the unaffected limb hidden d. Control condition: involved participants looking away from their stimulated limb with the unaffected limb hidden Dosage: 3 x 6-minute blocks of 24 stimuli were undertaken with a 3-minute rest period between blocks. Each treatment session involved 72 stimuli and lasted for 24 minutes. Frequency of administration: each participant received 4 sessions of each experimental condition in varying order (total of 16 sessions), with 3 to 4 days between sessions Provider: not reported
Outcomes	The trial authors assessed outcomes at baseline, immediately and 2 days post-treatment **Primary outcomes:** 2-point discrimination threshold, measured in mm, using a mechanical calliper **Secondary outcomes:** self-rated current pain (at rest) severity using a 100 mm VAS anchored with "no pain" and "worst possible pain"

Moseley 2009 *(Continued)*

Notes	**Source of funding:** Nuffield Oxford Medical Fellowship, NHMRC Senior Research Fellowship, Templeton Foundation **Statement regarding declarations of interest:** the authors declared no conflicts of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The conditions were randomised and counterbalanced so that each participant had four sessions of each condition, but in varying order". Comment: the trial authors did not report the method of sequence generation
Allocation concealment (selection bias)	Low risk	Comment: this was not applicable (when cross-over design employed).
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: given the nature of the intervention, participants were not blinded to treatment allocation but the extent to which the lack of blinding may have introduced bias is uncertain.
Blinding of outcome assessment (detection bias) Self-reported outcomes	Unclear risk	Comment: unblinded participants self-reported some outcomes (e.g. pain intensity) but the extent to which the lack of blinding may have introduced bias is uncertain.
Blinding of outcome assessment (detection bias) Investigator-administered outcomes	Unclear risk	Comment: we do not known whether or not the outcome assessors were blinded to the treatment condition.
Incomplete outcome data (attrition bias) Dropout rate described and acceptable	Low risk	Comment: the trial authors did not report any dropouts; they presented results based on the total number of included participants.
Incomplete outcome data (attrition bias) Participants analysed in the group to which they were allocated	Low risk	Comment: not applicable (when cross-over design employed).
Selective reporting (reporting bias)	High risk	Comment: the trial authors fully reported outcome data graphically for all outcomes; they did not report raw data in numerical form with measures of variation.
Sample size	High risk	Quote: "Ten patients with chronic CRPS of one hand or wrist (diagnosed according to Bruehl et al.) were recruited". Comment: the small sample size may have introduced bias in the estimates of treatment effect.
Duration of follow-up	High risk	Quote: "The TPD for the three sites was averaged to provide a measure at pre-training, post-training and 2 days later". Comment: the trial authors did not measure outcomes over a clinically relevant length of time.

Moseley 2009 *(Continued)*

Other bias	Unclear risk	Quote: "...there were 1–2 days between the follow-up assessment and the next training session. Participants were advised not to undertake tactile training in between sessions". Comment: the extent to which an interval of 1 to 2 days between outcome assessment and training sessions represented an adequate wash-out period, and therefore the extent to which a carry-over effect may have introduced bias in the estimates of treatment effect, is not known.

Mucha 1992

Study characteristics	
Methods	**Design:** parallel-group, 2-arm RCT. (The trial authors reported that participants in the control group crossed over into the experimental group. However, we deemed that this trial did not employ a true cross-over design and we analysed it as a 2-arm, parallel-group trial up to the endpoint just prior to cross-over). **Setting:** not reported (Germany; dates not reported) **Interventions:** CO_2 baths plus exercise therapy or exercise therapy alone **Sample size calculation:** not reported

Participants	**Number of participants:** 40 (20 per group)
	
	Type of noxious initiating event: post-trauma (no further details reported) (upper limb)
	
	Diagnostic criteria: acute algodystrophy of the hand (diagnostic criteria not reported)
	
	Baseline characteristics:
	
	Total sample (separate intervention and control group data not reported)
	
	Age range 47 to 56 years (group data not reported)
	
	Duration of CRPS (range) 2 to 6 weeks (group data not reported)
	
	1. CO_2 baths plus exercise therapy
	  a. Female:male = 13:7
	2. Exercise alone
	  a. Female:male = 11:9
	
	Inclusion criteria:
	
	1. CRPS I of the hand
	2. Post-traumatic onset
	3. "high active stage of condition"
	4. Minimum of 2 weeks duration of symptoms
	
	Exclusion criteria: more than 6 weeks duration of symptoms

Interventions	Those participants on medication prior to the trial were instructed to cease their medication at the start of the trial **CO_2 baths plus exercise (n = 20)** Components of intervention 1. CO_2 bath

Mucha 1992 *(Continued)*

2. After the bath, 30 to 45 minutes rest in an anti-swelling functional position
3. Exercise therapy (as below)

Dosage: 12 minute CO_2 bath with water temperature of 32 °C to 33 °C and a CO_2 concentration of 800 mg/L to 1000 mg/L

Frequency of administration: 5 times a week for 4 weeks (20 sessions)

Provider: not reported

Exercise (n = 20)

Components of intervention: progressive exercise therapy. The intensity was dependent on pain level and symptom behaviour.

Dosage: not reported

Frequency of administration: 5 times a week for 4 weeks (20 sessions)

Provider: not reported

Outcomes	The trial authors assessed outcomes at baseline and twice weekly until completion of the intervention period (4 weeks post recruitment). The trial authors did not state any primary outcomes. 1. Self-rated pain intensity at rest; measured using a graphic analogue scale (no scale reported) 2. Self-rated pain intensity at night; measured using a graphic analogue scale (no scale reported) 3. Self-rated pain intensity with movement; measured using a graphic analogue scale (no scale points reported) 4. Hand circumference: measured over the wrist, MCPs and DIPs, recorded in cm; probably difference between sides; only MCP data provided 5. Range of motion: neutral 0 method of forearm, hand and fingers, recorded in degrees, only wrist data reported 6. Grip strength: hand held dynamometer, relative to other side 7. Temperature: difference between sides; more than 0.8 degrees difference was recorded as positive
Notes	**Source of funding:** not reported **Statement regarding declarations of interest:** not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: " Patients were randomised into two groups". Comment: the trial authors did not report the method of sequence generation.
Allocation concealment (selection bias)	Unclear risk	Comment: the trial authors did not report the method of allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: given the nature of the intervention, participants were not blinded to treatment and may have had different expectations about the benefits of each intervention.
Blinding of outcome assessment (detection bias) Self-reported outcomes	High risk	Comment: unblinded participants, who may have had different expectations about the benefits of the intervention they received, self-reported some outcomes (e.g. pain intensity).

Mucha 1992 *(Continued)*

Blinding of outcome assessment (detection bias) Investigator-administered outcomes	Unclear risk	Comment: the trial authors did not report the statement of procedures regarding blinding of the outcome assessor.
Incomplete outcome data (attrition bias) Dropout rate described and acceptable	Low risk	Comment: there were no apparent dropouts.
Incomplete outcome data (attrition bias) Participants analysed in the group to which they were allocated	Low risk	Comment: the trial authors analysed participants in the group to which they were allocated but did not explicitly report the method of analysis (ITT versus per protocol).
Selective reporting (reporting bias)	High risk	Comment: the trial authors fully reported outcome data graphically for all outcomes; but did not report raw data in numerical form with measures of variation.
Sample size	High risk	Quote: "20 participants per group". Comment: the small sample size may have introduced bias in the estimates of treatment effect.
Duration of follow-up	High risk	Comment: comparison was only possible immediately at the end of the 4-week therapy session as the control group crossed over to the treatment arm at this point.
Other bias	Low risk	Quote: "Statistical testing showed homogeneity across both groups". Comment: there were no apparent baseline differences between groups. Comment: we did not identify any other sources of bias.

Oerlemans 1999

Study characteristics	
Methods	**Design:** parallel-group, 3-arm, single-blind RCT **Setting:** outpatient clinics of 2 university hospitals (The Netherlands; June 1994 to February 1998) **Interventions:** physical therapy (PT) plus medical treatment or occupational therapy (OT) plus medical treatment or minimal care plus medical treatment (control) **Sample size calculation:** the study planned to recruit 150 participants (50 per group) in order to be able to detect between-group differences of 6 to 7 points in the impairment level sum score (ISS) with 80% power
Participants	**Number of participants:** 135 (physical therapy group n = 44; OT group n = 44; SW (control) group n = 47) **Type of noxious initiating event:** mixed (fracture (53%), spontaneous onset (13%), contusion (11%), mallet finger, carpal tunnel syndrome, postoperative interventions, sprains (proportions not reported) (upper limb) **Diagnostic criteria:** Veldman 1993 (CRPS I)

Oerlemans 1999 *(Continued)*

Baseline characteristics:

1. PT:
   a. Mean (SD) age = 50.4 (15.6) years; female:male = 29:15
   b. Mean (SD) duration of CRPS I: 3.1 (3.4) months
2. OT:
   a. Mean (SD) age = 56.3 (17) years; female:male = 31:13
   b. Mean (SD) duration of CRPS I: 2.9 (2.5) months
3. SW:
   a. Mean (SD) age = 51.5 (16.9) years; female:male = 35:12
   b. Mean (SD) duration of CRPS I: 2.9 (3.1) months

Inclusion criteria:

1. CRPS I of 1 upper limb of less than 1 year duration
2. Participants could complete treatment at 1 of 2 study sites
3. Aged 18 years or older.

Exclusion criteria:

1. Impairment of contralateral extremity
2. Relapse of CRPS I
3. Pregnancy or lactation
4. Prior sympathectomy of the affected extremity

Interventions	All participants received medical treatment according to a fixed pre-established protocol, consisting of free-radical scavengers (dimethylsulfoxide (DMSO) 50% applied locally 5 times a day at the affected location or if DMSO-intolerant, N-acetylcysteine (600 mg 3 times a day), peripheral vasodilators in the case of primarily cold CRPS I (calcium entry blocker verapamil, sustained-release 240 mg once per day or ketanserine 20 mg twice per day eventually increased to 40 mg or pentoxifylline 400 mg twice per day) and treatment of trigger points. Participants also received general information regarding CRPS I; including advice to rest the extremity and not provoke pain. **PT (n = 44)** Components of intervention: 1. Intensity and form of treatment adjusted to the needs of each individual participant 2. Pain management advice/counselling directed towards helping participants gain control of the pain and optimise coping by offering insight, practical advice, and support and/or by relaxation exercises 3. Connective tissue massage, transcutaneous electric nerve stimulation (TENS), exercises for reducing the pain (details not reported) 4. Instruction, training and practising of skills by addressing compensatory activities and body positioning (details not reported) Dosage: 30 minutes per session (details for individual components not reported) Frequency of administration: adjusted to the needs of each individual participant (details not reported) Provider: physical therapists **OT (n = 44)** Components of intervention: 1. Intensity and form of treatment adjusted to the needs of each individual participant 2. Splinting 3. Desensitisation (tactile and proprioceptive) programme (details not reported) 4. Improving functional abilities of the arm/hand by executing various activities, while moving as normally as possible

Oerlemans 1999 *(Continued)*

5. Training to improve performance of activities of daily living (e.g. learning how to perform activities differently, advice regarding assistive devices)

Dosage: 30 minutes per session (details for individual components not reported)

Frequency of administration: adjusted to the needs of each individual participant (details not reported)

Provider: occupational therapists

Minimal care (n = 47)

Components of intervention:

1. Participants were given attention in the form of listening and insight into the social problems accompanying CRPS I
2. Advice regarding how not to evoke pain, rest and asking for help with performing activities perceived as excessively demanding

Dosage: 45 minutes per session

Frequency of administration: adjusted to needs of each individual participant (details not reported)

Provider: social workers

Outcomes

Outcomes, as reported across trial reports, variously assessed at baseline and at 6 weeks, 3 months, 6 months and 12 months post recruitment. The primary endpoint was the difference in impairment level sum score between baseline and 12 months post recruitment.

1. Self-rated pain intensity (present) using a VAS (0 to 100 scale, anchor points not reported)
2. Self-rated pain intensity (resulting from effort with the affected extremity) using a VAS (0 to 100 scale, anchor points not reported)
3. Self-rated pain intensity (least pain experienced in the preceding week) using a VAS (0 to 100 scale, anchor points not reported)
4. Self-rated pain intensity (worst pain experienced in the preceding week) using a VAS (0 to 100 scale, anchor points not reported)
5. McGill Pain Questionnaire (Dutch language version), including the: a. total pain rating index (PRI-T), b. total number of words chosen (NWC-T), c. number of 'sensory' words chosen (NWT-S), d. number of 'affective' words chosen (NWT-A), e. number of 'evaluative' words chosen (NWT-E)
6. Percentage of reduced normal mobility, measured by dividing the difference in active range of motion, as measured with a plastic transparent goniometer, between the joints (shoulder, elbow, wrist, digits) of the affected and unaffected upper limbs
7. Impairment rating (according to the Guides to the Evaluation of Permanent Impairment (GEPI): a composite score derived from a. measures of loss of active range of motion assessed using goniometry, b. sensory loss in the fingers and thumb assessed via 2-point discrimination testing and c. grip strength assessed by a dynamometer; with a maximum possible score of 60%, with higher scores indicating greater impairment (only measured at 12 months post-treatment; not measured at baseline)
8. Impairment level sum score (ISS): constructed to map alterations in impairment in RSD participants; formed by outcomes obtained with 4 measurement parameters and 5 instruments. The outcomes for each instrument are converted into a score, from which the compounded ISS is derived, including a. VAS pain/effort; b. McGill Pain Qr (NWC-T); c. active ROM (from 5 joints (wrist/fingers); d. temperature difference between hands; e. volume difference between hands. Score range was from 5 to 50, with higher scores indicating more severe 'impairment'.
9. The Radboud Skills Questionnaire; used to determine the perceived degree of deviation from normal use of both hands in activities of daily living (details regarding scoring and interpretation not reported)
10. The modified Greentest; used to measure differences in the degree to which both hands could move light objects (e.g. small pins, discs) within 15 seconds using different grips (details regarding scoring and interpretation not reported)
11. The Radboud Dexterity Test; used to make qualitative assessments of 7 skills associated with daily activities (e.g. closing a zip fastener, washing hands) (details regarding scoring and interpretation not reported)

Oerlemans 1999 *(Continued)*

12.Sickness Impact Profile (SIP) 36. The total score was computed (score range of 0 to 100) as well as the sub-scores for the degree of physical dysfunction and the degree of psychosocial dysfunction (details regarding scoring and interpretation not reported).

Notes	**Source of funding:** research grant from the National Health Insurance Board (Ziekenfondsraad), The Netherlands **Statement regarding declarations of interest:** not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned to one of three groups". Quote: "Randomisation was restricted to blocks of six". Quote: "Assignment to groups was performed according to allocation lists established by the Department of Medical Statistics of the University of Nijmegen". Comment: the trial authors used an acceptable method to generate the allocation sequence.
Allocation concealment (selection bias)	Unclear risk	Quote: "Assignment to groups was performed according to allocation lists established by the Department of Medical Statistics of the University of Nijmegen". Comment: the trial authors did not adequately report the method of allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: given the nature of the intervention, participants were not blinded to treatment and may have had different expectations about the benefits of each intervention.
Blinding of outcome assessment (detection bias) Self-reported outcomes	High risk	Comment: unblinded participants, who may have had different expectations about the benefits of the intervention they received, self-reported some outcomes (e.g. pain intensity).
Blinding of outcome assessment (detection bias) Investigator-administered outcomes	Unclear risk	Comment: we do not know if outcome assessors were blinded to treatment allocation when measuring percentage loss of joint mobility, impairment ratings, impairment level sum score and disability-based measures.
Incomplete outcome data (attrition bias) Dropout rate described and acceptable	Unclear risk	Quote: "After inclusion in the study, 44 patients were assigned to PT, 44 patients to OT and 47 patients to CT. In the course of the 1-year study period, seven, four and four patients abandoned the trial, respectively". Comment: whilst the overall dropout rate was acceptable (11%), there was an unequal dropout rate between groups (PT: 16%, OT: 9%, CT: 9%) and the trial authors did not report the reasons for dropping out.
Incomplete outcome data (attrition bias) Participants analysed in the group to which they were allocated	Low risk	Quote: "Two analyses were done: an intention-to-treat analysis (ITT) and a per-protocol analysis (PP). In the ITT analysis, outcomes of all the participants were used for the group they were originally assigned to. In the PP analysis, outcomes of protocol violators were ignored". Quote: "Three patients from the PT group could not complete the treatment protocol (so were protocol violators) but had test continuity".

Oerlemans 1999 *(Continued)*

		Comment: the trial authors presented limited data from both ITT and per protocol analyses for selected outcomes.
Selective reporting (reporting bias)	High risk	Comment: the trial authors reported limited and incomplete outcome data across 4 separate trial reports for self-reported pain and disability outcomes and for investigator-administered outcomes. Comment: no numerical data presented for 3 out of the 4 measures of self-rated pain intensity or percentage of reduced normal mobility outcomes. Comment: no numerical data reported for impairment rating. Comment: limited numerical data presented for ISS. Comment: no numerical data presented for the Radboud Skills Questionnaire, modified Greentest or Radboud Dexterity Test.
Sample size	High risk	Quote: "After inclusion in the study, 44 patients were assigned to PT, 44 patients to OT and 47 patients to CT". Comment: the small sample size may have introduced bias in the estimates of treatment effect.
Duration of follow-up	Low risk	Quote: "Re-assessment was performed 6 weeks (t1), 3 months (t2), 6 months (t3) and 12 months (t4) after inclusion in the study". Comment: the trial authors measured outcomes over a clinically relevant length of time.
Other bias	High risk	Quote: "If, during the period of the trial, the patient explicitly indicated that he or she wanted to switch to another adjuvant therapy, this was allowed. Using a coin, with heads or tails it was decided which adjuvant therapy was next". Quote: "Fourteen patients switched therapies: 12 from CT to PT (nine patients) or OT (three patients) and two from OT to PT". Comment: violations of the random sequence generation were permitted.

Ozcan 2019

Study characteristics	
Methods	**Design:** parallel, 2-arm single-blind RCT **Setting:** inpatient rehabilitation centre (Turkey; recruitment between April 2014 to March 2015) **Interventions:** conventional stroke rehabilitation programme plus fluidotherapy or conventional stroke rehabilitation programme alone **Sample size calculation:** a total sample size of 28 participants were necessary to detect a between-group difference of at least 2 painDETECT units with 0.80 power and 0.05 error
Participants	**Number of participants:** 32 (experimental group n = 16, control group n = 16) **Type of noxious initiating event:** hemiplegia following stroke (upper limb) **Diagnostic criteria:** Harden 2010 (CRPS I) **Baseline characteristics:** 1. Stroke rehabilitation plus fluidotherapy:

Ozcan 2019 *(Continued)*

a. Mean (SD) age = 62.61 (9.23) years; female:male = 10:5
b. Mean (SD) duration of CRPS I = not reported

2. Stroke rehabilitation:
a. Mean (SD) age = 63.46 (14.63) years; female:male = 8:7
b. Mean (SD) duration of CRPS I = not reported

Inclusion criteria:

1. Stroke of less than 12 months duration
2. Presence of subacute stage CRPS I resulting from a cerebrovascular accident
3. Mini-Mental State Examination score ≥ 23

Exclusion criteria:

1. Presence of neglect
2. Sensory or motor aphasia
3. Presence of shoulder subluxation
4. Unstable medical condition
5. Other causes of CRPS (postfracture, postsurgery and peripheral nerve injury)
6. Bilateral CPRS I
7. Psychotic disorders
8. Neuropathic pain syndromes
9. Open wounds in the treatment area

Interventions	All participants received a conventional stroke rehabilitation including neurophysiological treatment approaches, occupational therapy, physiotherapy (positioning, ROM, stretching, strengthening exercises, postural control, weight-shifting, gait training, endurance training, orthosis (if required) and education), and speech therapy (if required). Both groups also received conventional TENS (Everyway branded, EV-603M) to the hemiplegic upper extremity at a frequency of 100 hertz with 10 mA to 30 mA and 50 ms to 100 ms pulse duration. **Stroke rehabilitation plus fluidotherapy (n = 16)** Components of the intervention: 1. The patient washed the affected upper extremity and removed all jewellery and was positioned in a relaxed and comfortable position to allow treatment. 2. The affected extremity was inserted into the sleeve of a fluidotherapy device (Fizyoflug 2000 branded), which was fit snugly around the proximal arm. The therapy was delivered at a temperature of 40 °C for 20 minutes in continuous mode. 3. Patients were encouraged to do active ROM exercises with the wrist, metacarpophalangeal and interphalangeal joints if possible. Dosage: 2 to 4 hours of rehabilitation plus 20 minutes of fluidotherapy Frequency of administration: 5 days a week for 3 weeks (total 15 sessions) Provider: not reported **Stroke rehabilitation programme (n = 16)** Dosage: 2 to 4 hours a day Frequency of administration: 5 days a week for 3 weeks (total 15 sessions) Provider: not reported
Outcomes	The trial authors assessed outcomes at baseline and on completion of the intervention period. 1. Pain severity i) at rest and ii) while performing active range of motion exercises measured using a 10 cm VAS (0 = no pain to 10 = unbearable pain)

Ozcan 2019 *(Continued)*

2. Upper limb oedema using volumetric measurements of water displacement (in millilitres)
3. Neurological recovery using the Brunnstrom Motor Recovery Stages (BMRS), a 6-stage classification (1 = presence of flaccidity, incapability of voluntary movement; 2 = spasticity appears; 3 = increased spasticity, gaining minimal voluntary movement, control in synergy patterns; 4 = decreased spasticity, capability of voluntary movements out of synergy patterns; 5 = more decrease in spasticity, capability of more complex combinations of movements; 6 = disappearance of spasticity, capability of movement of individual joints, and almost normal co-ordination)
4. Functional status using the Functional Independence Measure (FIM) motor items scored on a 7-point ordinal scale ranging from 7 (complete independence) to 1 (complete dependence)
5. Presence and severity of neuropathic pain using the painDETECT questionnaire comprising 7 sensory symptom items for pain graded from 0 to 5, 1 item on the pain course pattern and 1 item on pain radiation, with total scores ranging from 0 to 38; scores of 19 to 38 indicate likely neuropathic pain, scores of 13 to 18 indicate unclear or possible neuropathic pain and scores of ≤ 12 indicate the characterisation of pain is more likely to be nociceptive

Notes	**Source of funding:** no funding was reported **Statement regarding declarations of interest:** none declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A computer-generated randomization program was used to randomly assign the patients to the control group or experimental group." Comment: it is likely that the trial authors used an acceptable method to generate the allocation sequence.
Allocation concealment (selection bias)	Unclear risk	Comment: the trial authors did not report the method of allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: given the nature of the intervention, participants were not blinded to treatment and may have had different expectations about the benefits of each intervention.
Blinding of outcome assessment (detection bias) Self-reported outcomes	High risk	Comment: unblinded participants, who may have had different expectations about the benefits of the intervention they received, self-reported some outcomes (e.g. VAS).
Blinding of outcome assessment (detection bias) Investigator-administered outcomes	Low risk	Quote: "Same investigator (U.H.T) who was blinded to group allocation performed the pre and post-treatment evaluations". Comment: the outcome assessor of objective outcomes was blinded to treatment allocation.
Incomplete outcome data (attrition bias) Dropout rate described and acceptable	Low risk	Quote: "During the rehabilitation program 1 patient from each group had to remove from the study because of the new onset unstable medical conditions. At last 15 patients in control group and 15 patients in experimental group completed the rehabilitation program and were included the final analysis". Comment: the minimal dropout rate (1 participant from each trial arm) is unlikely to have biased the results.
Incomplete outcome data (attrition bias)	High risk	Comment: the trial authors excluded 2 participants (1 from the fluidotherapy group and 1 from the control group) from the analysis because of the onset of unstable medical conditions, in violation of the ITT principle.

Ozcan 2019 *(Continued)*

Participants analysed in the group to which they were allocated		
Selective reporting (reporting bias)	High risk	Comment: the trial authors did not provide a study protocol and outcome measures are reported as median and range without measures of variance.
Sample size	High risk	Quote: "Considered the inclusion and exclusion criteria only 32 patients were eligible for study and they were randomly assigned to control and experimental group". Comment: the small sample size may have introduced bias in the estimates of treatment effect.
Duration of follow-up	High risk	Quote: "We evaluated the patients before and after a 3-week rehabilitation program". Comment: the trial authors did not measure outcomes over a clinically relevant length of time.
Other bias	Low risk	Comment: we did not identify any other sources of bias.

Ryan 2017

Study characteristics	
Methods	**Design:** parallel-group, placebo-controlled, 2-arm pilot RCT **Setting:** NHS Hospital (United Kingdom, dates not reported) **Interventions:** usual care physiotherapy plus transcutaneous electrical nerve stimulation (TENS) or placebo TENS **Sample size calculation:** since this was a feasibility study a sample size calculation was not undertaken
Participants	**Number of participants:** 8 (experimental group n = 6, control group n = 2) **Type of noxious initiating event:** not reported (upper limb) **Diagnostic criteria:** 'Budapest criteria' Harden 2010 (CRPS I) **Baseline characteristics:** 1. TENS (N = 6): a. Mean (range) age = 39 (32 to 50) years; female:male = 4:2 b. Mean (SD) duration of CRPS I = not reported 2. Placebo TENS (N = 2): a. Mean (range) age = 32.5 (29 to 36) years; female:male = 2:0 b. Mean (SD) duration of CRPS I = not reported **Inclusion criteria:** 1. ≥ 18 years 2. Diagnosis of CRPS I of the upper limb for ≥ 6 months (N.B. those who once fulfilled criteria but no longer did and had ongoing pain were also included) **Exclusion criteria:**

Ryan 2017 *(Continued)*

1. Finding TENS unacceptable or intolerable
2. Lacking capacity to give informed consent
3. Neurological conditions
4. Unable to speak English
5. Pacemaker implanted
6. Heart disease
7. Epilepsy
8. Pregnancy

Interventions	All participants received usual care physiotherapy including, but not limited to, advice, education, exercise, cognitive behavioural therapy, motor imagery, hand laterality recognition training, desensitising and hydrotherapy **TENS (n = 6)** Components of the intervention: patient self-administered, pulsed, synchronised dual channel TENS using a two-channel TENS unit (Elpha II 3000 muscle and pain stimulator, Danmeter) was applied to the upper arm proximal to the affected site Dosage: 20 pulses, delivered over a 1-second period (20 Hz stimulation frequency) with a non-stimulation interval of 5 seconds Frequency of administration: 90 minutes daily for 3 weeks (total number of sessions completed not reported) Provider: usual care physiotherapy was provided by a single physiotherapist and TENS was self-administered **Placebo TENS (n = 2)** Components of the intervention: the placebo group received TENS in an identical manner to the active intervention except that no electrical current was delivered. The power light flashed pulsatingly to indicate the device was switched on. Provider: usual care physiotherapy was provided by a single physiotherapist and placebo TENS was self-administered
Outcomes	The trial authors assessed outcomes at baseline, on the completion of the intervention period (3 weeks) and at 3 months: 1. Self-reported pain intensity (average pain over the last 2 days) measured using a VAS (length not specified) with anchor points of "no pain" to "worst imaginable pain" 2. Self-reported daily pain intensity measured 4 times a day using a 0 to 10 scale anchored with 0 "no pain" and 10 "worst imaginable pain" 3. Self-reported function measured using the Disabilities of the Arm, Shoulder and Hand (DASH), a 30-item questionnaire scaled from 0 to 100 (scale interpretation not reported) 4. Pain medication use 5. Adverse reactions
Notes	**Source of funding:** this study was supported by a research grant from the British Association of Hand Therapists **Statement regarding declarations of interest:** none declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Eligible participants provided informed consent and were randomly allocated to TENS or placebo TENS using a random number generator".

Ryan 2017 *(Continued)*

		Comment: the trial authors used an acceptable method to generate the allocation sequence.
Allocation concealment (selection bias)	Low risk	Quote: "Eligible participants provided informed consent and were randomly allocated to TENS or placebo TENS using a random number generator and prefilled concealed envelopes by a team member uninvolved in participant contact." Comment: the trial authors used an acceptable method to conceal the allocation sequence.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "The placebo group received TENS in an identical manner to the active intervention except that no electrical current was delivered, although the power light flashed pulsatingly indicating that the device was switched on. It was impossible to blind participants to receiving a strong non-painful TENS sensation." Quote: "Blinding the therapist was not possible". Comment: given the nature of the intervention, participants may not have been blinded to treatment and may have had different expectations about the benefits of each intervention. Personnel were not blinded and may have inferred different expectations about the benefits of each intervention.
Blinding of outcome assessment (detection bias) Self-reported outcomes	High risk	Quote: "It was impossible to blind participants to receiving a strong non-painful TENS sensation." Comment: the sham intervention did not control for the sensory characteristics of the real intervention and as such participants were not blinded to treatment and may have had different expectations about the benefits of each intervention. Quote: "At the three-month follow-up, all three of the participants from the TENS group who completed these questions were certain that their TENS unit was working correctly, while the one participant from the placebo group thought that the TENS unit was working correctly but was not certain". Comment: while trialists attempted to investigate patients' expectations and the validity of their single-blinding procedures, the dropout rate of 50% means they were not able to do this thoroughly.
Blinding of outcome assessment (detection bias) Investigator-administered outcomes	Low risk	Not applicable.
Incomplete outcome data (attrition bias) Dropout rate described and acceptable	High risk	Quote: "There was a 50% dropout rate with only four participants providing data at the three-month follow-up point". Comment: the high dropout rate may have introduced bias in the estimates of treatment effect.
Incomplete outcome data (attrition bias) Participants analysed in the group to which they were allocated	High risk	Comment: the method of analysis (ITT versus per protocol) was not reported. Comment: 2 out of 8 participants did not receive their allocated intervention.
Selective reporting (reporting bias)	Low risk	Comment: reported data were either presented graphically or incomplete.

Ryan 2017 *(Continued)*

		Comment: the authors supplied the missing data for our outcomes of interest on request.
Sample size	High risk	Quote: "Thirteen individuals initially showed interest in participating of whom eight consented and were randomised". Comment: the small sample size may have introduced bias in the estimates of treatment effect.
Duration of follow-up	Low risk	Quote: "VAS data were collected at baseline, post-treatment and at three-month follow-up" Comment: the trial authors measured outcomes over a clinically relevant length of time.
Other bias	High risk	Quote: "The imbalance in the randomisation was also an issue. The randomisation had been undertaken to ensure an equal number of 15 participants would be randomised to each group; however, by chance, the random sequence initially was loaded towards assigning more to the intervention group rather than the placebo group." Quote: "In addition, monitoring the number of usual care physiotherapy sessions was an important step with respect to monitoring co-interventions. The number of sessions varied quite considerably between participants". Comment: the trial groups were imbalanced and engagement with physiotherapy treatment differed between groups, which may have introduced bias in the estimates of treatment effects. Quote: "Those who once fulfilled the criteria, no longer did, but had ongoing pain were classed as CRPS-NOS (not otherwise specified) and were also included". Comment: including patients who no longer satisfied the trial's diagnostic criteria may have compromised the external validity of the findings.

Saha 2021

Study characteristics	
Methods	**Design:** parallel-group, 2-arm RCT **Setting:** out-patient rehabilitation centre (India, dates not reported) **Interventions:** mirror therapy plus stroke rehabilitation or stroke rehabilitation **Sample size calculation:** “In this study, expected effect size d was considered as 0.4. Sample size estimation yielded a sample size of 42, with significance level α = 0.05 and a power of study 80%”
Participants	**Number of participants:** 38 (19 in each group) **Type of noxious initiating event:** stroke (upper limb) **Diagnostic criteria:** shoulder-hand syndrome (i.e. post-stroke complex regional pain syndrome), (diagnostic criteria not reported) **Baseline characteristics:** 1. Stroke rehabilitation plus mirror therapy: a. Mean (SD) age = 57.40 (4.91) years; female:male = 5:10

Saha 2021 *(Continued)*

b. Mean (SD) duration of stroke 13.27 (2.02) months

2. Stroke rehabilitation:
   a. Mean (SD) age = 59.73 (6.11) years; female:male = 5:10
   b. Mean (SD) duration of stroke 13.47 (1.92) months

Inclusion criteria:

1. Patients aged between 50 to 70 with shoulder-hand syndrome
2. First-time stroke
3. Could follow the verbal commands

Exclusion criteria:

1. Any visual impairment causing difficulty in participating in mirror therapy
2. Any orthopaedic or neurological condition that may interfere with recovery of shoulder-hand syndrome
3. Recent myocardial infarction

Interventions	Participants in both groups received 4 weeks of conventional stroke rehabilitation comprising supervised neurodevelopmental facilitation techniques, range of motion exercises, stretching for elbow, wrist, fingers and task training of the upper extremity; 30 minutes a day, 5 days a week for 4 weeks **Stroke rehabilitation plus mirror therapy (n = 19)** Components of intervention: patients were seated on a chair or stool close to a mirror (55 cm x55 cm) positioned vertically between the patient's upper limbs. The unaffected limb was placed in front of the mirror, whereas the affected limb was placed in the opposite side of the mirror, which made it invisible. Whilst performing the same exercises as those in the 'Stroke rehabilitation' group (as detailed below) patients observed the mirror image of their unaffected limb as if it was their affected limb. All patients were instructed to attempt to perform the exercises bilaterally. Dosage: 30 minutes a day Frequency of administration: 5 days a week for 4 weeks (total of 20 sessions) Provider: physiotherapist **Stroke rehabilitation (n = 19)** Components of intervention: bilateral rhythmical flexion and extension of the shoulder and elbow, forearm supination and pronation, wrist flexion and extension, finger flexion and extension, fanning out the hand, finger and thumb abduction, making a fist and release, lateral prehension, pad to pad, pad to side grip, grasping objects, single finger movement and thumb opposition; stretching of shoulder retractors, elbow flexors, forearm pronators, wrist flexors and finger flexors through weight bearing on affected hand, and touching the opposite shoulder and head by affected hand. Instruction was given to the patients to keep the affected limb elevated during night as much as possible. Patients performed all the exercises of stroke rehabilitation programme, while directly visualising their both affected and unaffected limbs. Dosage: 30 minutes a day Frequency of administration: 5 days a week for 4 weeks (total of 20 sessions) Provider: physiotherapist
Outcomes	Outcomes assessed at baseline, after treatment and 2 weeks post-treatment. The trial authors did not state any primary outcome. 1. Self-rated pain intensity using a 0 to 10 numeric rating scale (0 = no pain, 10 = worst pain ever) 2. Self-rated disability using the Functional Independence Measure (FIM) (scoring properties not fully reported. Assumed score range 18 to 126, with lower scores indicating worse disability)

Saha 2021 *(Continued)*

3. Oedema measured by figure-of-eight measurement method. A standard 1/4th-inch wide tape measure was used to perform figure-of-eight measurements of hand size (in cm).

Notes	**Source of funding:** not reported **Statement regarding declarations of interest:** none declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients (n = 38) were randomly allocated by sealed, numbered envelopes with the randomization sequence, into two equal groups, Group A (control group) and Group B (experimental group)". Comment: the trial authors did not report the method of sequence generation.
Allocation concealment (selection bias)	Low risk	Quote: "Patients (n = 38) were randomly allocated by sealed, numbered envelopes with the randomization sequence, into two equal groups, Group A (control group) and Group B (experimental group)". Comment: the trial authors probably used an acceptable method to conceal the allocation sequence.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: given the nature of the intervention, participants were not blinded to treatment and may have had different expectations about the benefits of each intervention.
Blinding of outcome assessment (detection bias) Self-reported outcomes	High risk	Comment: unblinded participants, who may have had different expectations about the benefits of the intervention they received, self-reported some outcomes (e.g. pain intensity).
Blinding of outcome assessment (detection bias) Investigator-administered outcomes	High risk	Quote: "All the evaluations were carried out by the same physiotherapist, who have supervised the therapy, so there was no blinding to group allocation". Comment: outcome assessors were unblinded to participant group allocation.
Incomplete outcome data (attrition bias) Dropout rate described and acceptable	High risk	Quote: "Initial sample of 38 patients witnessed five dropouts along the course of the study. Thirty-three patients (Group A [n = 17], Group B [n = 16]) completed the 4-week supervised stroke rehabilitation program and participated in postintervention evaluation. Three patients were lost to follow-up and hence 30 patients (Group A [n = 15] and Group B [n = 15]) were included for the statistical analyses" Quote: "A plausible limitation of this study is the dropouts due to inability to continue intervention and also missed follow-up by a considerable number of patients". Comment: an overall dropout rate of 21% may have introduced bias in the estimates of treatment effect.
Incomplete outcome data (attrition bias) Participants analysed in the group to which they were allocated	High risk	Quote: "As reasons for dropout were nonclinical, so a per-protocol analysis instead of an intention-to-treat analysis, was used during the statistical analysis to see the effect of interventions if patients were fully compliant". Comment: violation of the principle of ITT analysis may have introduced bias in the estimates of treatment effect.

Saha 2021 *(Continued)*

Selective reporting (reporting bias)	Low risk	Comment: outcome data were adequately reported for all outcomes reported in the methods section of the publication.
Sample size	High risk	Quote: "…hence 30 patients (Group A [n = 15] and Group B [n = 15]) were included for the statistical analyses". Comment: the small sample size may have introduced bias in the estimates of treatment effect.
Duration of follow-up	Unclear risk	Quote: "Evaluations were done at baseline, immediately after 4-week intervention and during follow-up after 2-week postintervention". Comment: the clinical relevance of a 2-week follow-up of outcomes is uncertain.
Other bias	Low risk	Comment: we did not identify any other sources of bias.

Sarkar 2017

Study characteristics	
Methods	**Design:** parallel-group, 3-arm, single-blind RCT **Setting:** urban pain referral centre (India; recruitment from January 2016 to June 2016) **Interventions:** anti-neuropathic medicine and contrast baths or anti-neuropathic medicine and exercise or anti-neuropathic medicine and mirror therapy **Sample size calculation:** not reported
Participants	**Number of participants:** 30 (10 in each group) **Type of noxious initiating event:** aetiology not reported (upper and lower limb) **Diagnostic criteria:** 'Budapest criteria' Harden 2007 (CRPS type not reported) **Baseline characteristics:** not reported **Inclusion criteria:** 1. Patients diagnosed with CRPS according to the Budapest Criteria 2. Age: 18 to 70 years 3. Patients having signs and symptoms for more than 6 weeks but less than 1 year 4. Patients already treated with neuropathic medicine for at least 4 weeks **Exclusion criteria:** 1. Radiculopathy or pain in single nerve distribution in the extremity 2. Infection or cellulitis and other local pathologies 3. Autonomic nervous system disease 4. Peripheral nerve disease 5. Vascular conditions such as vascular insufficiency, deep vein thrombosis, lymphedema, and erythromelalgia
Interventions	All participants received anti-neuropathic medicines (gabapentin 900 mg daily in 3 divided doses and amitriptyline 10 mg daily) **Contrast baths (n = 10)**

Sarkar 2017 *(Continued)*

	Components of the intervention: patients were asked to immerse the affected body part (hand/foot) in cold and hot water (tolerable) alternatively for 3 minutes and 1 minute, respectively. Procedures started and ended with cold water immersion. Dosage: 15 minutes per session Frequency of administration: details not reported Provider: not reported **Exercise (n = 10)** Components of the intervention: patients were seated comfortably keeping a nonreflecting board or curtain perpendicular to his or her midline with the unaffected limb facing the non-reflective surface and affected limb hidden. Patients were asked to do exercises of the unaffected limb attending to the non-reflective surface, which was followed by their painful limb (if possible). The following movements were practised: • Upper extremity: wrist flexion, extension, ulnar deviation and radial deviation and metacarpophalangeal and interphalyngeal joint movements including making and releasing a fist and opponens movements. • Lower extremity: ankle plantar flexion and dorsiflexion, inversion and eversion, and toe (at metatarsophalangeal and tarsophalangeal joints) flexion and extension Dosage: 2 minutes of exercise followed by 2 minutes of rest, for 20 minutes Frequency of administration: twice per day (duration of intervention period not explicitly reported) Provider: not reported **Mirror therapy (n = 10)** Components of the intervention: patients were asked to sit comfortably keeping a mirror perpendicular to the midline with the unaffected side in front of the reflecting surface of mirror and the affected side hidden behind the mirror. The affected limb was relaxed and rested on a support surface behind the mirror throughout. Patients were asked to look at the mirror and assume that the mirror image of unaffected side was the affected body part. Patients performed exercises (not fully reported) of the unaffected body part in a full and pain free range in all directions front of the mirror. By seeing the mirror image patients imagined the affected limb was moving in pain-free manner. Dosage: 2 minutes of exercise followed by 2 minutes of rest, for 20 minutes Frequency of administration: twice per day (duration of intervention period not explicitly reported) Provider: not reported
Outcomes	Outcomes assessed at baseline, and at 1, 2 and 4 weeks within the intervention period. No follow-up post intervention. 1. Self-reported pain at rest using an 11-point NRS; 0 = no pain, 10 = the highest pain the patient can imagine 2. Self-reported pain on movement (details not reported) using an 11-point NRS; 0 = no pain, 10 = the highest pain the patient can imagine 3. Swelling, measured using the 'figure of 8' method (in cm)
Notes	**Source of funding:** no funding was provided **Statement regarding declarations of interest:** the authors declared no conflicts of interest

Risk of bias

Bias	Authors' judgement	Support for judgement

Sarkar 2017 *(Continued)*

Random sequence generation (selection bias)	High risk	Quote: "The patients were asked to draw a chit from a jar containing 30 chits (10 chits for each group), and they were randomly allocated into following three groups containing ten patients in each group". Comment: the trial authors used a non-random sequence generation process.
Allocation concealment (selection bias)	Unclear risk	Comment: the trial authors did not adequately report the method of allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: given the nature of the intervention, participants were not blinded to treatment and may have had different expectations about the benefits of each intervention.
Blinding of outcome assessment (detection bias) Self-reported outcomes	High risk	Comment: unblinded participants, who may have had different expectations about the benefits of the intervention they received, self-reported some outcomes (e.g. pain intensity).
Blinding of outcome assessment (detection bias) Investigator-administered outcomes	Low risk	Quote: "The progression and outcome of each subject were recorded by an independent investigator (single-blinded study– blinded at the level of investigator)". Comment: outcome assessors were blinded to participants' group allocation.
Incomplete outcome data (attrition bias) Dropout rate described and acceptable	Unclear risk	Comment: not reported.
Incomplete outcome data (attrition bias) Participants analysed in the group to which they were allocated	Unclear risk	Comment: the method of analysis (ITT versus per protocol) was not reported.
Selective reporting (reporting bias)	Low risk	Comment: the trial authors reported outcome data for all outcomes reported in the methods section of the publication but reported the standard error of the mean rather than the standard deviation. Comment: the authors supplied the missing data for our outcomes of interest on request.
Sample size	High risk	Quote: "A total 30 patients were selected". Comment: the small sample size may have introduced bias in the estimates of treatment effect.
Duration of follow-up	Unclear risk	Comment: not adequately reported.
Other bias	Unclear risk	Comment: baseline sample demographics and characteristics not reported.

Schreuders 2014

Study characteristics	
Methods	**Design:** parallel-group, 2-arm, single-blind RCT

Schreuders 2014 *(Continued)*

Setting: not reported (The Netherlands; dates not reported)

Interventions: GMI programme plus conventional treatment or conventional treatment alone

Sample size calculation: not reported

Participants	**Number of participants:** 18 (experimental group n = 11, control group n = 7) **Type of noxious initiating event:** not reported (upper limb) **Diagnostic criteria:** Bruehl 1999 (CRPS I) **Baseline characteristics:** 1. GMI programme (and included in the analysis N = 10): a. Mean (SD) age = 42.4 (16.8) years; female:male = 8:2 b. Mean (SD) duration of CRPS I: 50.3 (53.7) months 2. Standard care (and included in the analysis N = 5): a. Mean (SD) age = 52.8 (12.7) years; female:male = 4:1 b. Mean (SD) duration of CRPS I: 127.4 (87.5) months **Inclusion criteria:** 1. Aged between 18 and 75 years 2. Symptoms > 6 months **Exclusion criteria:** not reported
Interventions	All participants received conventional treatment including a 6-week OT and physiotherapy programme, including training of grip function, muscle strengthening and joint mobility interventions, writing exercises and advice to reduce the use of splints. Participants were asked not to participate in other treatment programmes during the 12-week period and not to change the type or dosage medication of their medication unless instructed to do so by their physician. **GMI programme (n = 11)** Components of intervention: 1. Adapted from Moseley 2004 2. Hand laterality recognition (1 week) 3. Visual movement imagery exercises (1 week) 4. Mirror therapy (4 weeks) Dosage: 10 minutes Frequency of administration: every hour (3 times per day minimum) for a total of 6 weeks Provider: therapists (distinction between physio- and occupational therapist not reported) **Standard care (n = 7)** Components of intervention: 1. Supervised exercise (first 3 weeks) 2. Feedback regarding home exercises (second 3 weeks) 3. Training of grip functions (details not reported) 4. Muscle strengthening exercises (details not reported) 5. Joint mobility (details not reported) 6. Housekeeping and other daily activities (details not reported) 7. Writing exercises 8. Coaching to reduce the use of splints

Schreuders 2014 *(Continued)*

	Dosage: 60 minutes per week (over 1 or 2 sessions) Frequency of administration: 1 or 2 sessions per week, for 6 weeks Provider: physical therapists and occupational therapists
Outcomes	Outcomes were assessed at baseline and after 3, 6 (immediately post-treatment) and 12 weeks (6 weeks post-treatment) post enrolment **Primary outcomes:** 1. Self-rated current pain intensity using a VAS ranging from 0 (no pain) to 100 (unbearable pain) 2. Self-rated minimum pain intensity (last 3 days) using a VAS ranging from 0 (no pain) to 100 (unbearable pain) 3. Self-rated maximum pain intensity (last 3 days) using a VAS ranging from 0 (no pain) to 100 (unbearable pain) 4. Activities of daily living using the Radboud Skills Questionnaire (RASQ) total score and 3 sub-scales: a. Clothing, washing, eating b. Household activities c. Recreation, social activities **Secondary outcomes:** fine hand co-ordination of both hands by using the Nine Hole Peg Test (recorded in seconds)
Notes	**Source of funding:** ErasmusMC Mrace Project Zorg 2004-20, grant number 2004-20 **Statement regarding declarations of interest:** the trial authors declared no conflicts of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Based on a computerized random schedule..." Comment: the trial authors used an acceptable method to generate the allocation sequence.
Allocation concealment (selection bias)	Low risk	Quote: "Based on a computerized random schedule, a researcher not involved in the execution of the trial, made a sequence of numbered opaque envelopes. These envelopes were prepared with equality being achieved after every ten subjects (block size 10)". Quote: "Envelopes were given in sequence of entry to the patient and were opened by the patient". Comment: the trial authors used an acceptable method to conceal the allocation sequence.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Patients were not blinded to the treatment as they were aware of the treatment content". Comment: given the nature of the intervention, participants were not blinded to treatment and may have had different expectations about the benefits of each intervention.
Blinding of outcome assessment (detection bias) Self-reported outcomes	High risk	Comment: unblinded participants, who may have had different expectations about the benefits of the intervention they received, self-reported some outcomes (e.g. pain intensity).
Blinding of outcome assessment (detection bias)	Low risk	Quote: "The assessor was blinded for the allocation to the experimental or control group".

Schreuders 2014 *(Continued)*

Investigator-administered outcomes		Quote: "The measurements were performed by trained blinded assessors". Comment: the trial authors blinded outcome assessors to participant group allocation
Incomplete outcome data (attrition bias) Dropout rate described and acceptable	High risk	Comment: the trial authors did not adequately report the dropout rate in the 'Results' section of the manuscript. Comment: according to 'Figure 2' of the manuscript, 1 participant was lost to follow-up and 2 discontinued the intervention from the experimental group, 1 participant withdrew after randomisation, 1 participant was lost to follow-up and 3 discontinued the intervention from the conventional treatment group, giving dropout rates of 27% and 71% respectively, and an overall dropout rate of 44%. Comment: the high dropout rate may have introduced bias in the estimates of treatment effect.
Incomplete outcome data (attrition bias) Participants analysed in the group to which they were allocated	High risk	Comment: the trial authors reported analysis as ITT in Figure 2 of the unpublished manuscript. Quote: "Three patients (one in the experimental group, two in the control group) could not be included in the analysis due to insufficient compliance in filling out the VAS and RASQ questionnaires or because of immediate withdrawal from the control therapy because the participants only wanted the graded MIP". Comment: violation of the principle of ITT analysis may have introduced bias in the estimates of treatment effect. Quote: "From seven of the remaining fifteen patients (five in the experimental group and two in the control group) there were missing end-tests" (i.e. at 12 weeks post enrolment/6 weeks postintervention). Quote: "Differences in changes in both groups over times were tested using a generalized estimating equations (GEE) approach. Under the assumption that missing data were random and not due to group allocation or treatment effect, this model estimates missing data values, thereby allowing the use of data from all participants, irrespective of whether they were measured at all time points". Comment: use of GEE may have introduced bias in the estimates of treatment effect.
Selective reporting (reporting bias)	High risk	Comment: the trial authors reported outcome data graphically for all self-reported pain outcomes and did not report raw data in numerical form with measures of variation. The trial authors presented effect sizes with measures of variation for the Radboud Skills Questionnaire and Nine Hole Peg Test and did not report numerical data with measures of variation.
Sample size	High risk	Quote: "For this trial eighteen patients were included". Quote: "For this study only 18 patients were assessed for eligibility and only 15 of them could be included in the analysis. The number of patients in the study was therefore too small to detect possible effects with the intended power for which 52 patients were needed". Comment: the small sample size may have introduced bias in the estimates of treatment effect.
Duration of follow-up	Unclear risk	Quote: "Outcome was assessed at baseline, after 3, 6 and 12 [i.e. 6 weeks post-treatment] weeks".

Schreuders 2014 *(Continued)*

		Comment: the clinical relevance of a 6-week follow-up of outcomes is uncertain.
Other bias	High risk	Comment: baseline data for 3 participants excluded from the analysis not reported. Comment: likely highly significant baseline imbalance in duration of symptoms between groups.

Strauss 2021

Study characteristics	
Methods	**Design:** cross-over group, 2-arm RCT **Setting:** University Medical Centre; recruitment via support groups (Germany; from 2019 to 2020) **Interventions:** graded motor imagery or wait-list control **Sample size calculation:** "Statistical power calculations were based on the outcome parameter "pain" from the study of Moseley, 2006. Here, the GMI training showed an improvement of 23.4 mm (range: 16.2−30.4 mm) on a 100mm VAS whereas the control group (physiotherapy without GMI) showed only an improvement of 10.5 mm (range: 1.9−19.2 mm). A resulting effect size of 1.29 (G*power) with alpha 0.05 and power 0.95 (one-tailed) resulted in 9 participants per treatment group. In addition a 15% dropout rate for longitudinal studies had to be added. Because the results of Moseley, 2006 were considered rather optimistic, the group size of the current study was planned for about 25 participants for inclusion in the study and about 22 participants for final analysis of treatment effect."
Participants	**Number of participants:** 22 (numbers randomised to each phase not reported; baseline data for only 20 of 22 participants reported) **Type of noxious initiating event:** mixed (carpal tunnel surgical intervention (25%), 'cervical spine' (10%), 'other surgery' (40%), wrist fracture (20%), not reported (5%)) (upper limb) **Diagnostic criteria:** unilateral CRPS type II (diagnostic criteria not reported) **Baseline characteristics:** Total sample (separate data by treatment phase not reported): 1. Mean (SD) age = 54.7 (14.5) years); female:male = 17:3 2. Mean (SD) duration of CRPS II 61 (43) months **Inclusion criteria:** 1. Aged 18 to 80 years 2. Diagnosis of unilateral CRPS-II of the upper limb for ≥ 6 months **Exclusion criteria:** 1. Spread of symptoms to other limbs 2. Brain damage 3. Severe other neurological or psychiatric diagnoses 4. Other severe pain syndromes
Interventions	**Graded motor imagery** Components of intervention: 3 sequential treatment stages (left/right judgements, imagined movements, mirror therapy) each lasting 2 weeks. The first 2 stages were performed with the 'Recognise Hand' app (Neuro Orthopaedic Institute, Australia). The mirror therapy stage was performed with a

Strauss 2021 *(Continued)*

	foldable mirror and a set of cars with images of hands in different positions. For left/right judgements, patients were asked to classify whether images showed a left or right hand. For imagined movements, patients were asked to mentally match the exact hand posture shown in the picture. For mirror therapy, patients were asked to perform movements displayed on the cards with their non-affected hand first while observing it in the mirror, and then increasing the intensity of the tasks by using objects and coactivating the affected hand that remained in the mirror box. Dosage: at least 10 minutes every waking hour Frequency of administration: 7 days a week for 6 weeks Provider: not reported **6-week waiting period** Components of intervention: not reported
Outcomes	Outcomes were assessed at baseline, after treatment phase 1 at 6 weeks, and after treatment phase 2 at 12 weeks. The trial authors did not state any primary outcome. 1. Self-rated pain intensity for the affected limb i) at rest and ii) on movement using a 10 cm visual analogue scale (0 = not at all, 10 = unbearable) 2. Functional impairment using the Disabilities of Arm, Shoulder and questionnaire (details regarding scoring and interpretation not reported) (baseline only) 3. CRPS severity using the CRPS Severity Score (details regarding scoring and interpretation not reported) 4. Depressive symptoms using the Beck's Depression Inventory II (details regarding scoring and interpretation not reported) (baseline only)
Notes	**Source of funding: "**ML was supported by the National Institute for Health & Collaborative Research Australia for travel to Adelaide (Memorise Grand) and the DFG (LO 795/28-1). NN received local funding from the exchange program of the University of Greifswald (International Office). SS was awarded a Gerhard-Domagk fellowship for undertaking this study; he also received a grant by the Else Kroner Fresenius-Stiftung 2019-A24, which enabled to support JH and SB during their doctoral thesis." **Statement regarding declarations of interest:** "ML receives financial reimbursement for editing a Neuroscience journal by the Thieme Verlag. GLM has received support from: ConnectHealth UK, Seqirus, Kaiser Permanente, Workers' Compensation Boards in Australia, Europe and North America, AIA Australia, the International Olympic Committee, Port Adelaide Football Club, Arsenal Football Club. Professional and scientific bodies have reimbursed him for travel costs related to presentation of research on pain at scientific conferences/symposia. He has received speaker fees for lectures on pain and rehabilitation. He receives book royalties from NOIgroup publications, Dancing Giraffe Press & OPTP for books on pain and rehabilitation. The funding organizations did not have an impact on the design of the study and the results reported here."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "participants were randomly allocated to one of 2 groups; random group 1 started with the 6-week training period after the baseline parameters had been collected. After 6 weeks of GMI therapy in random group 1, a 6 week waiting period followed. Random group 2 started with a 6- week waiting period and continued with the 6-week GMI therapy." Comment: the trial authors did not report the method of sequence generation.
Allocation concealment (selection bias)	Unclear risk	Quote: "participants were randomly allocated to one of 2 groups; random group 1 started with the 6-week training period after the baseline parameters had been collected. After 6 weeks of GMI therapy in random group 1, a 6 week

Strauss 2021 *(Continued)*

		waiting period followed. Random group 2 started with a 6- week waiting period and continued with the 6-week GMI therapy." Comment: the trial authors did not report the method of allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: given the nature of the intervention, participants were not blinded to treatment and may have had different expectations about the benefits of each intervention.
Blinding of outcome assessment (detection bias) Self-reported outcomes	High risk	Comment: unblinded participants, who may have had different expectations about the benefits of the intervention they received, self-reported some outcomes (e.g. pain intensity).
Blinding of outcome assessment (detection bias) Investigator-administered outcomes	Unclear risk	Quote: "Effects (behavioural measures and fMRI) over groups were evaluated by an evaluator blinded for the GMI or waiting period." Comment: it is unclear whether the authors considered the CRPS Severity Score a 'behavioural' measure' and as such it is unclear whether the outcome assessor for this outcome was blinded.
Incomplete outcome data (attrition bias) Dropout rate described and acceptable	Unclear risk	Quote: "Twenty-six CRPS patients were included for the intervention study. Twenty-two finished measurements as planned but 2 of these could not come to the post MRI assessment after GMI intervention, because of the onset of SARS-CoV-2 (corona virus) pandemic in March 2020." Comment: the extent to which an overall dropout rate of 15% may have introduced biased estimates of treatment effect is uncertain.
Incomplete outcome data (attrition bias) Participants analysed in the group to which they were allocated	High risk	Quote: "Twenty-six CRPS patients were included for the intervention study. Twenty-two finished measurements as planned, but 2 of these could not come to the post MRI assessment after GMI intervention, because of the onset of SARS-CoV-2 (corona virus) pandemic in March 2020. Therefore, in the final group analysis we included 20 patients diagnosed with CRPS". Comment: the method of analysis was not reported for clinical outcomes. The trial authors excluded 6 participants in violation of the ITT principle.
Selective reporting (reporting bias)	Low risk	Comment: outcome data for pain intensity and CRPS Severity Score were inadequately reported after treatment phases and DASH was only reported at baseline. Comment: the authors supplied the missing data for our outcomes of interest on request.
Sample size	High risk	Quote: "Twenty-six CRPS patients were included for the intervention study. Twenty-two finished measurements as planned". Comment: the small sample size may have introduced bias in the estimates of treatment effect.
Duration of follow-up	High risk	Quote: "participants were randomly allocated to one of 2 groups; random group 1 started with the 6-week training period after the baseline parameters had been collected. After 6 weeks of GMI therapy in random group 1, a 6 week waiting period followed. Random group 2 started with a 6- week waiting period and continued with the 6-week GMI therapy. After each time period, clinical and neurophysiological parameters were assessed". Comment: the trial authors did not measure outcomes over a clinically relevant length of time.

Strauss 2021 *(Continued)*

Other bias	High risk	Quote: "…we investigated 20 CRPS patients in a wait-list crossover design with 3 evaluation time points. Patients underwent a 6 week GMI treatment and a 6 week waiting period in a randomized group assignment…" Comment: in the trial registry the study is variously described as 'non-interventional', 'observational' and a 'non-randomised controlled trial' (https://drks.de/drks_web/navigate.do?navigationId=trial.HTML&TRIAL_ID=DRKS00017214). Comment: in the trial report the trial authors did not state any primary outcome. In the trial registry the primary outcome is specified as 'Pain intensity (visual analogue scale, after the 6 weeks training period)'. Comment: differences in descriptions of the trial design and specification of a primary outcome measure between the trial registration and the published trial report may have introduced bias. Comment: the absence of a washout period between treatment periods allows for potential differential carryover effects that may have biased estimates of treatment effect.

Topcuoglu 2015

Study characteristics

Methods	**Design:** parallel-group, 2-arm RCT **Setting:** Ankara Physical Medicine and Rehabilitation Education and Research Hospital (Turkey; recruitment between March 2009 to September 2009) **Interventions:** physiotherapy plus upper extremity aerobic exercise or physiotherapy alone **Sample size calculation:** not reported
Participants	**Number of participants:** 40 (20 in each group) **Type of noxious initiating event:** hemiplegia following stroke (upper limb) **Diagnostic criteria:**Bruehl 1999 (CRPS I) **Baseline characteristics:** 1. Physiotherapy plus upper extremity aerobic exercise: a. Mean (SD) age = 65.95 (8.7) years; female:male = 9:11 b. Mean (SD) duration of CRPS I = not reported 2. Physiotherapy: a. Mean (SD) age = 67.5 (11.2) years; female:male = 9:11 b. Mean (SD) duration of CRPS I = not reported **Inclusion criteria:** 1. Diagnosis of hemiplegia associated with a cerebrovascular event that took place at least 1 month and at most 6 months prior to the study 2. Diagnosed CRPS on the hemiplegic side **Exclusion criteria:** 1. Aphasia 2. Serious mental disorders

Topcuoglu 2015 *(Continued)*

	3. Diseases that could hinder the upper arm ergonometry aerobic exercise programme (fracture, surgery to the extremity, serious restriction of joint motion, serious cardiovascular disease or pressure sores) 4. A history of fracture accounting for CRPS 5. Unco-operative 6. Unable to balance while sitting for 20 minutes
Interventions	All participants received medical treatment and physiotherapy programmes for CRPS and stroke rehabilitation. The CRPS physiotherapy programme included TENS (shoulder-hand region encompassing the painful region (100 Hz frequency, 20 min per day)), cold pack (20 minutes per day), retrograde massage and contrast baths, The comprehensive stroke physiotherapy programme included therapeutic exercises, neurophysiological exercises, postural exercises, balance and co-ordination exercises and exercises of activities of daily living. The medical treatment included diclofenac Na (twice per day) and paracetamol (4 times per day) (doses not reported). **Physiotherapy plus upper extremity aerobic exercise (n = 20)** Components of the intervention: arm crank ergonometry using a 35 cm-diameter upper arm ergonometer with adjustable resistance (MONARK, Riverside, CA, USA) Dosage: upper extremity aerobic exercise was performed at 5 watts per minute for 30 minutes Frequency of administration: physiotherapy frequency not reported; upper extremity aerobic exercise was performed 5 days a week for 4 weeks Provider: doctor in cardiopulmonary rehabilitation **Physiotherapy (n = 20)** Dosage and frequency of administration: not reported
Outcomes	The trial authors assessed outcomes at baseline and on completion of the intervention period. **Primary outcomes:** 1. Self-reported pain severity for the shoulder and the hand i) during the day, ii) during the night and iii) upon movement, measured using a 10 cm VAS (anchor points not reported) 2. CRPS clinical determinants (hyperaesthesia, allodynia, pain on movements, oedema in the hand, and range of motion of shoulder and wrist) (methods of assessment not reported) **Secondary outcomes:** 1. Quality of life measured using the Nottingham Health Profile (NHP) (measurement properties not reported) 2. Depressive mood measured using the Beck Depression Scale (measurement properties not reported) 3. Motor level measured using Brunnstrom's Staging for the upper extremity and the hand (measurement properties not reported) 4. Spasticity measured using the Modified Ashworth Scale (measurement properties not reported) 5. Level of independence measured using the Functional Independence Measure (FIM) (measurement properties not reported)
Notes	**Source of funding:** no funding received **Statement regarding declarations of interest:** the authors declared no conflicts of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed using computer-generated numbers and the treatment group was assigned by the system."

Topcuoglu 2015 *(Continued)*

		Comment: the trial authors used an acceptable method to generate the allocation sequence.
Allocation concealment (selection bias)	Unclear risk	Comment: the trial authors did not report the method of allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: given the nature of the intervention, participants were not blinded to treatment and may have had different expectations about the benefits of each intervention.
Blinding of outcome assessment (detection bias) Self-reported outcomes	High risk	Comment: unblinded participants, who may have had different expectations about the benefits of the intervention they received, self-reported some outcomes (e.g. VAS).
Blinding of outcome assessment (detection bias) Investigator-administered outcomes	Unclear risk	Quote: "Four weeks later after the treatment ended, the assessments were repeated by the same assessor physician, who was unaware of the patient's group assignment." Comment: the outcome assessor of investigator-administered outcomes was blinded to treatment allocation.
Incomplete outcome data (attrition bias) Dropout rate described and acceptable	Low risk	Comment: the trial authors did not report any information regarding the presence or absence of dropouts or a study participant flowchart but all randomised participants were accounted for in the analyses.
Incomplete outcome data (attrition bias) Participants analysed in the group to which they were allocated	Unclear risk	Comment: the method of analysis (ITT versus per protocol) was not reported.
Selective reporting (reporting bias)	High risk	Comment: the trial authors did not provide a study protocol and reported incomplete outcome data for measures of pain. Only one of the continuous outcome measures was reported using point estimates and measures of variance.
Sample size	High risk	Quote: "The study included 40 patients with CRPS I after stroke". Comment: the small sample size may have introduced bias in the estimates of treatment effect.
Duration of follow-up	High risk	Quote: "These assessments were performed at baseline week 0 and after the end of the program week 4.". Comment: outcomes were not measured over a clinically relevant length of time.
Other bias	Low risk	Comment: we did not identify any other sources of bias.

Uher 2000

Study characteristics	
Methods	**Design:** parallel-group, 2-arm RCT **Setting:** not reported (Germany, dates not reported)

Uher 2000 *(Continued)*

	Interventions: manual lymph drainage (MLD) plus exercise or exercise alone **Sample size calculation:** not reported
Participants	**Number of participants:** 40 (15 in the manual lymph drainage group, 25 in the exercise alone group) **Type of noxious initiating event:** mixed (postfracture n = 27, post dislocation n = 9, postsurgery n = 4) (lower limb) **Diagnostic criteria:** CRPS I (diagnostic criteria not reported) **Baseline characteristics:** Total sample: female:male 31:4 1. Group receiving manual lymph drainage plus exercise: a. Mean (SD) age = not reported; female:male = not reported b. Mean (SD) duration of CRPS I = not reported 2. Group receiving exercise: a. Mean (SD) age = not reported; female:male = not reported b. Mean (SD) duration of CRPS I = not reported **Inclusion criteria:** 1. Clinical, radiographic and scintigraphic signs of CRPS 1 2. < 6 months post-trauma/surgery **Exclusion criteria:** 1. Venous insufficiency 2. Recurrent thrombophlebitis 3. Peripheral vascular disease 4. Blood disorders 5. Currently receiving physical treatment
Interventions	Participants were given a brochure providing general advice (details not reported), no analgesic or anti-inflammatory medication prescribed, participants were asked to inform the clinician if they took analgesia or anti-inflammatory medication for more than 3 days. **Manual lymph drainage plus exercise (n = 15)** Components of intervention: 1. Manual lymph drainage (further details not reported) 2. Exercise (as below) Dosage: 30 minutes Frequency of administration: 3 times per week for 6 weeks (18 sessions) Provider: physiotherapists **Exercise (n = 25)** Components of intervention: 1. Goal to improve range of motion and reduce pain 2. Rhythmic stabilisation techniques of Klein Vogelbach and passive movements as tolerated of the affected ankle Dosage: 30 minutes Frequency of administration: 3 times per week for 6 weeks (18 sessions)

Uher 2000 *(Continued)*

	Provider: physiotherapists
Outcomes	Outcomes assessed at baseline and immediately on completion of the intervention period (6 weeks post recruitment). The trial authors did not state any primary outcome. 1. Self-rated pain intensity measured using a 6-point verbal rating scale (0 = no pain, 5 = maximum pain) 2. Range of motion (dorsiflexion and plantarflexion) at the talocrural joint measured using a goniometer 3. Temperature measured using a surface thermometer, between the malleoli, with the value recorded as the difference between 2 sides 4. Swelling measured as the difference in ankle circumference (in cm), at level of malleoli, between 2 sides 5. Radiological assessment (details not reported) 6. Scintigraphic assessment (details not reported)
Notes	**Source of funding:** not reported **Statement regarding declarations of interest:** not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: the trial authors did not report the method of sequence generation.
Allocation concealment (selection bias)	Low risk	Quote: "Randomisation was done using the sealed envelope method, by a doctor not involved in the study". Comment: the trial authors used an acceptable method to conceal the allocation sequence.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: given the nature of the intervention, participants were not blinded to treatment and may have had different expectations about the benefits of each intervention.
Blinding of outcome assessment (detection bias) Self-reported outcomes	High risk	Comment: unblinded participants, who may have had different expectations about the benefits of the intervention they received, self-reported some outcomes (e.g. pain intensity).
Blinding of outcome assessment (detection bias) Investigator-administered outcomes	Low risk	Quote: "Tested by a doctor who did not know group assignment". Comment: the outcome assessor was blinded to treatment allocation.
Incomplete outcome data (attrition bias) Dropout rate described and acceptable	Low risk	Comment: an overall, and balanced, dropout rate of 12% is unlikely to have biased the results.
Incomplete outcome data (attrition bias) Participants analysed in the group to which they were allocated	High risk	Comment: the trial authors excluded three participants (2 from the MLD group and 1 from the exercise group) from the analysis because they did not regularly attend for therapy, in violation of the ITT principle. Two participants from the exercise group were excluded after randomisation secondary to wrongful inclusion despite fulfilment of exclusion criteria.
Selective reporting (reporting bias)	High risk	Comment: the trial authors did not report outcome data for pain intensity.

Uher 2000 *(Continued)*

Sample size	High risk	Comment: the small sample size may have introduced bias in the estimates of treatment effect.
Duration of follow-up	High risk	Quote: "Assessment after six weeks of therapy". Comment: outcomes were re-measured on immediate completion of the intervention period only and were not measured over a clinically relevant length of time.
Other bias	Low risk	Comment: we did not identify any other sources of bias.

Vural 2016

Study characteristics	
Methods	**Design:** parallel, 2-arm, single-blind RCT **Setting:** training and research hospital (Turkey; recruitment between November 2011 to September 2012) **Interventions:** conventional stroke rehabilitation programme plus mirror therapy or conventional stroke rehabilitation programme alone **Sample size calculation:** calculated with an assumed difference in post-treatment VAS score of 1.2 between groups. A total sample size of 28 (14 study participants and 14 controls) was necessary for a 2-sided test with statistical power of 0.90 and an alpha level of 0.05.
Participants	**Number of participants:** 30 (15 in each group) **Type of noxious initiating event:** hemiplegia following stroke (upper limb) **Diagnostic criteria:** Veldman 1993 (CRPS I) **Baseline characteristics:** 1. Mirror therapy plus stroke rehabilitation: a. Mean (SD) age = 68.9 (10.5) years; female:male = 7:8 b. Mean (SD) duration of CRPS I = not reported 2. Stroke rehabilitation: a. Mean (SD) age = 61.4 (11.9) years; female:male = 6:9 b. Mean (SD) duration of CRPS I = not reported **Inclusion criteria:** 1. First episode of hemiplegia after stroke diagnosed by a neurologist within 12 months 2. Concomitant dystrophic stage of CRPS I 3. Mini-Mental State Examination score > 23 **Exclusion criteria:** 1. Unstable medical status 2. Visual impairment 3. Shoulder subluxation 4. Shoulder injection in the preceding 6 months 5. Presence of neglect 6. Alternate explanation for upper limb pain 7. Concomitant progressive central nervous system disorder

Vural 2016 *(Continued)*

	8. History of hand dysfunction in the affected side
Interventions	All participants received a patient-specific conventional stroke rehabilitation programme consisting of neurodevelopmental facilitation techniques, occupational therapy, physiotherapy and speech therapy (if required). **Mirror therapy (n = 15)** Components of the intervention: 1. The patient was seated on a chair close to a table with a mirror (35 cm x 35cm) positioned vertically between the patient's upper limbs. The unaffected arm was placed in front of the mirror and the affected arm was placed in box, which made it invisible. 2. Patients were trained to perform various movements of the unaffected side: flexion and extension of the elbow, wrist, and fingers; supination and pronation of the forearm; abduction, adduction, and finger opposition. Patients were asked to look in the mirror during the exercise and imagine that the reflection belonged to the affected side. 3. Patients were told to try to do the same movements with the unaffected side. Dosage: 2 to 4 hours of rehabilitation plus 30 minutes of mirror therapy Frequency of administration: 5 days a week for 4 weeks (total 20 sessions) Provider: not reported **Stroke rehabilitation programme (n = 15)** Dosage: 2 to 4 hours a day Frequency of administration: 5 days a week for 4 weeks (total 20 sessions) Provider: not reported
Outcomes	The trial authors assessed outcomes at baseline and on completion of the intervention period. 1. Self-reported pain severity measured using a VAS (length not specified) with anchor points of 0 = "no pain" to 10 = "worst imaginable pain" 2. Motor recovery using the Brunnstrom Recovery Stages, which classifies recovery into 6 categories (1 = flaccidity; 2 = appearance of spasticity; 3 = increased spasticity, appearance of basic synergy patterns and minimal voluntary movements; 4 = decreased spasticity and movements out of synergy patterns; 5 = further decrease in spasticity, more complex combinations of movement, and synergy patterns that no longer dominate; 6 = disappearance of spasticity, being able to move individual joints and coordination almost normal) 3. Motor function using the Fugl-Meyer Assessment (FMA) wrist and hand subsections, with each subsection consisting of 12 items (5 for the wrist, 7 for the hand); each item is rated on a 3-point ordinal scale (0 = cannot perform, 1 = partially perform, 2 = completely perform) 4. Basic physical and cognitive function using the Functional Independence Measure motor items, with the degree of assistance scored from 1 "complete dependence" to 7 "complete independence" and total scores ranging from 13 to 91 (total measurement properties not reported) 5. Spasticity using the Modified Ashworth Scale (MAS) scored on a 6-point Likert scale with scores ranging from 0 (no increase in muscle tone) to 4 (limb rigidity during flexion or extension)
Notes	**Source of funding:** not reported **Statement regarding declarations of interest:** not reported

Risk of bias

Bias	Authors' judgement	Support for judgement

Vural 2016 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned to the mirror therapy group or the control group using computer-generated random numbers" Comment: the trial authors used an acceptable method to generate the allocation sequence.
Allocation concealment (selection bias)	Unclear risk	Comment: the trial authors did not report the method of allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: given the nature of the intervention, participants were not blinded to treatment and may have had different expectations about the benefits of each intervention.
Blinding of outcome assessment (detection bias) Self-reported outcomes	High risk	Comment: unblinded participants, who may have had different expectations about the benefits of the intervention they received, self-reported some outcomes (e.g. VAS).
Blinding of outcome assessment (detection bias) Investigator-administered outcomes	Low risk	Quote: "The assessments were performed by the same investigator (S.P.V.), who was blinded to group allocation." Comment: the outcome assessor of investigator-administered outcomes was blinded to treatment allocation.
Incomplete outcome data (attrition bias) Dropout rate described and acceptable	Low risk	Comment: all randomly assigned participants completed the study (as displayed in the published report's 'Flow diagram').
Incomplete outcome data (attrition bias) Participants analysed in the group to which they were allocated	Unclear risk	Comment: the method of analysis (ITT versus per protocol) was not reported.
Selective reporting (reporting bias)	High risk	Comment: the trial authors did not provide a study protocol and outcome measures are reported as median and range without measures of variation.
Sample size	High risk	Quote: "According to these criteria, 30 patients were eligible for the study." Comment: the small sample size may have introduced bias in the estimates of treatment effect.
Duration of follow-up	High risk	Quote: "We evaluated the clinical outcome scales only twice, before and 4 weeks after the therapy, and did not include follow-up evaluation". Comment: the trial authors did not measure outcomes over a clinically relevant length of time.
Other bias	Low risk	Comment: we did not identify any other sources of bias.

Abbreviations: CRPS I: complex regional pain syndrome type 1; CT: control therapy; GMI: graded motor imagery; IFC: interferential current; ITT: intention to treat; MIP: motor imagery programme; MLD: manual lymphatic drainage; NPS: neuropathic pain scale; NRS: numerical rating scale; OT: occupational therapy; PT: physiotherapy/physical therapy; RCT: randomised controlled trial; RSD: reflex sympathetic dystrophy; SD: standard deviation; SGB: stellate ganglion block; SPSS: Statistical Package for the Social Sciences; SW: social work; TDT: tactile discrimination training; TENS: transcutaneous electrical nerve stimulation; TPD: two-point discrimination; US: ultrasound; VAS: visual analogue scale.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bolel 2006	This study only evaluated the outcome measure of 'sympathetic skin response' and fell outside the inclusion criteria of this review
David 2015	Not a RCT Previously registered as a RCT (NCT 01915329) in the original review ('Characteristics of ongoing studies' table) (Smart 2016)
den Hollander 2020	Not a RCT
Dimitrijevic 2018	The study authors evaluated 'infrared thermography' and 'hand oedema' as outcome measures, which fell outside the inclusion criteria of this review
Fialka 1992	Not a RCT
Fialka 1996	Autogenic training does not fall within the scope of practice of physiotherapy
Field 1993	Not a RCT
Gromo 1974	Not a RCT
Jasmina 2012	Not a RCT
JPRN-UMIN000027348	Not a RCT (cross-over, non-randomised); originally identified in a trial registry Trial terminated early secondary to the transfer of a researcher (personal communication: Prof. Naoki Aizu, 8 August 2020)
Karabegović 2009	Not a RCT
Kocić 2010	The study authors evaluated 'infrared thermovision' as the only outcome measure, which fell outside the inclusion criteria of this review
Kotiuk 2019	The study authors evaluated 'body perception disturbance' as the only outcome measure, which fell outside the inclusion criteria of this review
Liao 2006	Acupuncture does not fall within the scope of practice of physiotherapy as defined in our protocol (Smart 2013)
Marianne 2015	Not a RCT Previously registered as a RCT (NCT01915329) in the original review ('Characteristics of ongoing studies' table) (Smart 2016)
NCT02667717	Originally identified in a trial registry. Trial terminated early secondary to difficulties recruiting patients and an apparent lack of effect from the experimental intervention (intermediate analysis). Observations reported by the primary investigator included: 1) 27 from a target of 88 participants had been recruited at the point of early termination, 2) after an intermediate statistical analysis it was found that there was a significant pain improvement in both groups but without any differences between groups and that the clinical improvement was maintained after 16 weeks in both groups, 3) there were no serious adverse events, 4) patients and practitioners found the experimental intervention interesting but too time consuming (personal communication: Dr Christelle Créac'h, 6 August 2020).
Perrigot 1982	Not a RCT

Study	Reason for exclusion
Solcà 2018	Not a RCT
Toth 2014	The trial included participants (N = 54) with mixed aetiologies but only 2 participants with complex regional pain syndrome (CRPS) with 1 randomised to each trial arm. We could not make any meaningful comparison.
Tulgar 1991	Not a RCT
Wu 1999	Qigong does not fall within the scope of practice of physiotherapy
Zyluk 1994	Not a RCT

Abbreviations: RCT: randomised controlled trial.

Characteristics of studies awaiting classification *[ordered by study ID]*

Dimitrijevic 2019

Methods	Not yet assessed
Participants	Not yet assessed
Interventions	Not yet assessed
Outcomes	Not yet assessed
Notes	The findings from this trial are currently only available as a conference abstract

Dimitrijevic 2020

Methods	Not yet assessed
Participants	Not yet assessed
Interventions	Not yet assessed
Outcomes	Not yet assessed
Notes	The findings from this trial are currently only available as a conference abstract

ISRCTN39729827

Methods	Not yet assessed
Participants	Not yet assessed
Interventions	Not yet assessed
Outcomes	Not yet assessed

ISRCTN39729827 *(Continued)*

Notes	As of 18 August 2020 we were unable to make contact with the author for an update of this trial's progress

ISRCTN97144266

Methods	Not yet assessed
Participants	Not yet assessed
Interventions	Not yet assessed
Outcomes	Not yet assessed
Notes	As of 30July 2020 we were unable to make contact (email delivery failure) with the author for an update of this trial's progress. We note that this trial was registered in 2005 and now assume that it is unlikely ever to be published.

Mallikarjunaiah 2015

Methods	Not yet assessed
Participants	Not yet assessed
Interventions	Not yet assessed
Outcomes	Not yet assessed
Notes	The findings from this trial are currently only available as a conference abstract

NCT01944150

Methods	Not yet assessed
Participants	Not yet assessed
Interventions	Not yet assessed
Outcomes	Not yet assessed
Notes	Originally identified in a trial registry and included as a trial in the 'Classification of ongoing studies' table in the original review (Smart 2016). As of 30 July 2020 we were unable to make contact (email delivery failure) with the author for an update of this trial's progress. We note that this trial was registered in 2013 and now assume it is unlikely ever to be published.

Patru 2017

Methods	Not yet assessed

Patru 2017 *(Continued)*

Participants	Not yet assessed
Interventions	Not yet assessed
Outcomes	Not yet assessed
Notes	The findings from this trial are currently only available as a conference abstract

UKCRN ID 12602

Methods	Parallel-group, 2-arm RCT (UK)
Participants	**Inclusion criteria:** 1. Diagnosed with CRPS type I **Exclusion criteria:** 1. Diagnosed with any other neurological, psychopathologic, motor disorder or major nerve damage (CRPS II) 2. The presence of any other limb pathology or pain on the affected CRPS limb 3. Cutaneous damage on the area to be stimulated 4. Receiving intensive CRPS-specific MDT rehabilitation in an inpatient setting during the time course of the study or within the previous month 5. Unable to understand written or verbal English and give informed consent
Interventions	**Experimental group:** ESDT and de-sensitisation tasks **Active comparator group:** routine care, including de-sensitisation tasks
Outcomes	1. Short form McGill Pain Questionnaire 2. Brief Pain Inventory questionnaire 3. Disability of Arm, Shoulder and Hand questionnaire (upper limb CRPS) 4. Lower Extremity Functional Scale questionnaire (lower limb CRPS) 5. Hospital Anxiety and Depression Scale 6. Adverse events
Notes	As of 30 July 2020, the author updated us via email that this trial is delayed

CRPS: complex regional pain syndrome; ESDT: electrical sensory discrimination therapies; RCT: randomised controlled trial

Characteristics of ongoing studies *[ordered by study ID]*

ChiCTR1900020835

Study name	Manual lymphatic drainage combined with transcranial magnetic stimulation for post-stroke type I complex regional pain syndrome: an exploratory clinical study
Methods	Parallel-group, 2-arm RCT (China)
Participants	**Inclusion criteria:** 1. Age 40 to 80 years, male or female

ChiCTR1900020835 *(Continued)*

	2. According to the "Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke in China" (2014 edition), diagnosed as cerebral infarction; diagnosed as cerebral haemorrhage according to "Guidelines for the diagnosis and treatment of Chinese cerebral hemorrhage" (2014 edition) 3. Comply with the CRPS diagnostic criteria proposed by the IASP (Budapest standard) 4. CRPS classification is type I (without peripheral nerve injury) 5. CRPS progress period: within 6 months 6. The vital signs are stable, without serious speech and cognitive impairments, which can be easily communicated and can be combined with rehabilitation therapy 7. Voluntary signing of informed consent and willingness to participate in this study **Exclusion criteria:** 1. Peripheral nerve injury or disease history 2. History of external injuries, fractures and muscle tendon injuries in the affected limbs 3. Limb thrombosis on the affected side 4. History of rheumatic diseases 5. Serious infections such as erysipelas 6. Severe cardiovascular, respiratory, liver and kidney diseases, unstable clinical symptoms 7. History of tumour disease 8. Severe malnutrition 9. Contraindications for MLD and rTMS 10. Participating in other relevant clinical research at the same time 11. Pregnancy
Interventions	**Experimental group:** routine rehabilitation and MLD and rTMS **Active comparator group:** routine rehabilitation
Outcomes	**Primary outcome measures:** 1. Hand volume 2. Degree of pain 3. Motor function 4. Mental status
Starting date	January 2019
Contact information	Dr Bai Yulong, dr_baiyl@fudan.cn; Qiu Xiao, qiuxiaoabc@126.com
Notes	As of 17 August 2020 we were unable to make contact with the author for an update of this trial's progress

CTRI/2019/01/017272

Study name	Efficacy of an integrated approach encompassing pregabalin and mirror therapy in management of complex regional pain syndrome type 1-a pilot study
Methods	Parallel-group, 2-arm RCT (India)
Participants	**Inclusion criteria:** 1. Budapest criteria of CRPS for clinical use **Exclusion criteria:**

CTRI/2019/01/017272 *(Continued)*

	1. The presence of pain at any other site due to any other cause 2. An intra-articular injection into the joints during the previous 6 months or use of systemic corticosteroids during the previous 4 months 3. Uncontrolled co-morbid medical conditions 4. Cognitive impairments that might interfere with understanding instructions for various questionnaires, motor testing and treatment
Interventions	**Experimental group:** cap pregabalin 75 mg BD (twice per day), scrub descrub therapy and mirror therapy **Active comparator group:** cap pregabalin 75 mg BD and scrub descrub therapy
Outcomes	**Primary outcome measures:** 1. Proportion of patients achieving NRS pain score of ≤ 3/10 at various designated intervals of time and neuropathic component of pain using NPSI scores **Secondary outcome measures:** 1. NRS-sleep score 2. Degrees of resolution of oedema and motor/trophic changes in affected limb 3. SF-12 questionnaire scores 4. Modulation of mRNA gene expression of mTORC1 and IL-6 genes
Starting date	January 2019
Contact information	Anish Malik, anishmalik14@yahoo.com
Notes	As of 17 August 2020 we were unable to make contact with the author for an update of this trial's progress

JPRN-UMIN000029801

Study name	The effectiveness of graded mirror therapy based on the assessment of mirrored limb perception to the patients with complex regional pain syndrome
Methods	Parallel-group, 2-arm RCT (Japan)
Participants	**Inclusion criteria:** (not specified) **Exclusion criteria:** 1. Patients with psychiatric disorder
Interventions	**Experimental group:** graded mirror therapy **Active comparator group:** conventional mirror therapy
Outcomes	**Primary outcome measures:** 1. Pain intensity **Secondary outcome measures:** (not specified)
Starting date	June 2019
Contact information	Akira Mibu, a_mibu@konan-wu.ac.jp

JPRN-UMIN000029801 *(Continued)*

Notes	As of 18 August 2020 the author updated us via email that this trial is ongoing and delayed secondary to the spread of COVID-19 infection

NCT02395211

Study name	Effects of proprioceptive stimulation under visual feedback in patient with CRPS: an exploratory study
Methods	Parallel-group, 2-arm RCT (Italy)
Participants	**Inclusion criteria:** 1. Age > 18 years and < 85 years 2. Diagnosis of stroke < 6 months prior to study enrolment 3. Diagnosis of complex regional pain syndrome according to Budapest criteria **Exclusion criteria:** 1. Neurological or psychiatric pathology 2. Severe cardio-pulmonary, renal, hepatic diseases 3. Pregnancy
Interventions	**Experimental group:** Gloreha device **Active comparator group:** usual physiotherapy
Outcomes	**Primary outcome measures:** 1. Visual analogue scale **Secondary outcome measures:** 1. Neuropathic Pain Symptom Inventory 2. McGill Pain Questionnaire 3. Erasmus MC modification to the (revised) Nottingham Sensory Assessment - Italian version 4. Fugl-Meyer Upper Extremity 5. Pressure Pain Threshold
Starting date	January 2015
Contact information	Dr Sofia Straudi, sofia.straudi@gmail.com
Notes	As of 30 July 2020 the author updated us via email that this trial is ongoing

NCT02753335

Study name	A randomized trial of patients with complex regional pain syndrome comparing graded motor imagery and desensitization versus simple desensitization and changes in resting-state connectivity of cerebral networks before and after treatment
Methods	Randomised cross-over design
Participants	**Inclusion criteria:**

NCT02753335 *(Continued)*

	1. Patients 18 to 70 years old. For patients who only participate in the clinical RCT (without fMRI) no upper age limit. 2. CRPS affecting one single upper or lower limb diagnosed by the IASP (2012) Budapest research criteria (Harden et al, 2010) 3. Triggering trauma or the onset of pain > 3 months ago **Exclusion criteria:** 1. Drug abuse 2. Malignant/progressive, systemic or neurodegenerative disease 3. Other severe pain conditions 4. Severe clinical anxiety or depression, symptoms of fatigue or ME of a disabling level For patients who participate in the MRI related analyses: 1. Metallic implants incompatible with the MR technology or medical condition not recommended for fMRI 2. Pregnancy 3. Phobia for MRI examination 4. Diseases that can cause structural changes and interfere with the interpretation of the MRI-scans (like severe diabetes mellitus, heart disease, ischaemic stroke and vascular conditions)
Interventions	**Experimental group:** graded motor imagery and desensitisation **Active comparator group:** desensitisation
Outcomes	**Primary outcome measures:** 1. Group difference in pain intensity 2. Change from baseline in intra-network connectivity in the Default Mode Network **Secondary outcome measures:** 1. Change from baseline in pain intensity 2. Group difference in CRPS Severity Score 3. Change from baseline in CRPS Severity Score 4. Group difference in Quick DASH score/percent lower extremity functional scale score 5. Relative change from baseline in Quick DASH/lower extremity functional scale score 6. Group difference in responder rate 7. Change from baseline in responder rate
Starting date	April 2016
Contact information	Lena Danielsson, lena.danielsson@unn.no
Notes	As of 24 August 2020, the author updated us via email that this trial is ongoing

NCT03377504

Study name	Clinical evaluation of the effects of mirror therapy in patients with complex regional pain syndrome (CRPS) type 1: prospective randomized single blind controlled study
Methods	Parallel-group, 2-arm RCT (Turkey)
Participants	**Inclusion criteria:**

NCT03377504 *(Continued)*

	1. Adult individuals over 18 years of age 2. CRPS type 1 diagnosis according to 2003 Budapest diagnostic criteria 3. Patients who developed CRPS type 1 due to traumatic causes (surgical procedures, fractures, immobilisation) 4. Patients who agree to participate in the study and sign the informed consent form **Exclusion criteria:** 1. Patients with peripheral nerve injuries (those with a diagnosis of CRPS type 2 according to Budapest criteria) 2. Patients with CRPS type 1 after central nervous system injury (stroke) 3. Patients in the acute and post-acute rehabilitation who have had primary or secondary tendon repair of the hand 4. The presence of comorbid conditions (e.g. decompensated heart failure, chronic renal insufficiency, malignancy) that would impair the functioning of the person and the health-related quality of life 5. The presence of comorbid disease affecting hand function (e.g. rheumatoid arthritis, psoriatic arthritis or other inflammatory diseases that cause hand involvement) 6. Patients with acute deep venous thrombosis and arterial thrombosis of the upper extremity 7. Patients with arterial/venous injury and/or undergoing arterial revascularisation 8. Patients with excessive alcohol and inappropriate opioid use 9. Patients with untreated psychiatric problems (major depression, anxiety, schizophrenia, etc.) 10. Patients with recurrent CRPS type 1
Interventions	**Experimental group:** mirror therapy and routine physical therapy **Active comparator group:** routine physical therapy
Outcomes	**Primary outcome measures:** 1. Pain severity (0 to 10 numeric rating scale (NRS)) **Secondary outcome measures:** 1. Grip strength (Jamar dynamometer) 2. Lateral pinch strength (pinchmeter) 3. Hand circumference measurements 4. Hand dexterity (Moberg pick up test) 5. Hand function in daily living activities (Cochin Hand Function Scale (CHFS)) 6. Health-related quality of life (Nottingham Health Profile (NHP))
Starting date	March 2017
Contact information	Dr Ayşe Adile Küçükdeveci, ayse.kucukdeveci@gmail.com. Ankara University. Faculty of Medicine, İbn-i Sina Research and Application Hospital, Ankara, Turkey, 06030).
Notes	As of 6 August 2020, the author updated us via email that this trial is completed and being analysed

NCT03887962

Study name	Trial of virtual reality biofeedback in patients with motor neglect from chronic pain or cerebrovascular disease
Methods	Parallel-group, 2-arm RCT (UK)

NCT03887962 *(Continued)*

Participants	**inclusion criteria:** 1. Patients with a diagnosis of stroke (of any cause), traumatic brain injury or chronic pain condition of more than 3 months duration (e.g. back and referred leg pain; complex regional pain syndrome; fibromyalgia) who are undergoing an inpatient or out-patient rehabilitation programme 2. Motor neglect as assessed by standard clinical examination by a physiotherapist trained to detect such motor neglect. This is defined as weakness and functional impairment without a loss of strength, reflexes or sensation. **Exclusion criteria:** 1. Patients with active serious medical problems that might affect their ability to participate in the exercise protocol (e.g. ongoing sepsis; recent myocardial infarction) 2. Patients who are unable to use treadmill safely as judged by the screening physiotherapist 3. Patients who are unable to give informed consent, either through issues relating to competency or to language 4. Patients with significant previous experience of virtual reality rehabilitation
Interventions	**Experimental group:** virtual environment feedback **Active comparator group:** control intervention
Outcomes	**Primary outcome measures:** 1. Distance walked (machine-reported) 2. Lower Extremity Functional Index **Secondary outcome measures:** 1. Brief Pain Inventory 2. Human Activity Profile 3. Hospital Anxiety and Depression Scale 4. Neglect Like Symptom Questionnaire 5. Satisfaction questionnaire 6. Machine-reported average stride length 7. Machine-reported number of steps 8. Machine-reported gait symmetry 9. Machine-reported gait timing
Starting date	May 2017
Contact information	Dr Nicholas Shenker
Notes	As of 30 July 2020 the author updated us via email that this trial is completed and being analysed

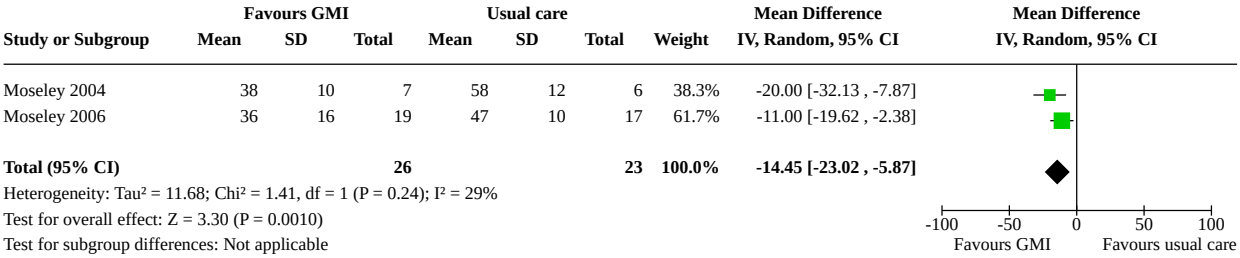
Abbreviations: ESDT: electrical sensory discrimination therapies; PGIC: patient global impression of change; RCT: randomised controlled trial; RSS: repetitive electrical sensory discrimination; TENS: transcutaneous electrical nerve stimulation; UK: United Kingdom; VAS: visual analogue scale.

DATA AND ANALYSES

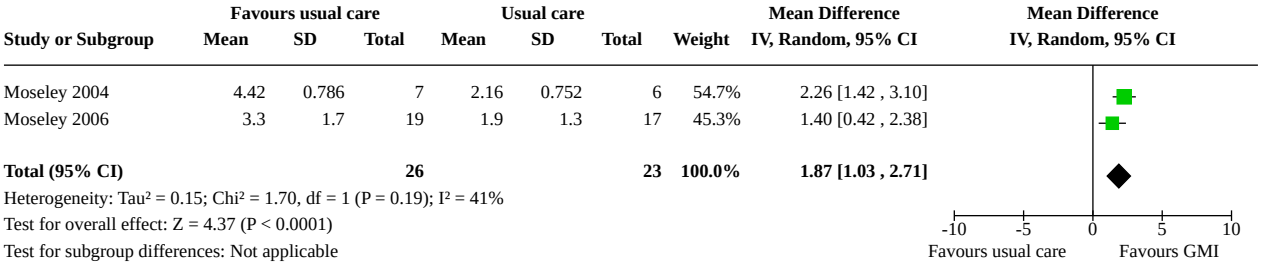
Comparison 1. Graded motor imagery versus standard care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Pain intensity (0 to 100 VAS; higher scores indicate worse pain) (post-treatment)	2	49	Mean Difference (IV, Random, 95% CI)	-14.45 [-23.02, -5.87]
1.2 Disability (0 to 10 patient-specific functional scale; higher scores indicate better function) (post-treatment)	2	49	Mean Difference (IV, Random, 95% CI)	1.87 [1.03, 2.71]

Analysis 1.1. Comparison 1: Graded motor imagery versus standard care, Outcome 1: Pain intensity (0 to 100 VAS; higher scores indicate worse pain) (post-treatment)



Analysis 1.2. Comparison 1: Graded motor imagery versus standard care, Outcome 2: Disability (0 to 10 patient-specific functional scale; higher scores indicate better function) (post-treatment)



APPENDICES

Appendix 1. Search strategies 2015

CENTRAL, DARE and HTA strategy

#1 MeSH descriptor: [Complex Regional Pain Syndromes] explode all trees

#2 "complex regional pain syndrome*":ti,ab,kw (Word variations have been searched)

#3 crps:ti,ab,kw (Word variations have been searched)

#4 (Post traumatic near/1 (algodystrophy or dystrophy or neurodystrophy or osteoporosis or pain syndrome)):ti,ab,kw (Word variations have been searched)

#5 "Minor causalgia":ti,ab,kw (Word variations have been searched)

#6 "Transient migratory osteoporosis":ti,ab,kw (Word variations have been searched)

#7 "Peripheral trophneurosis":ti,ab,kw (Word variations have been searched)

#8 ((Major or mitchell*) near/1 causalgia):ti,ab,kw (Word variations have been searched)

#9 "Neurovascular dystrophy":ti,ab,kw (Word variations have been searched)

#10 "Sudecks Osteodystrophy":ti,ab,kw (Word variations have been searched)

#11 Sympathalgia:ti,ab,kw (Word variations have been searched)

#12 Chronic traumatic oedema:ti,ab,kw (Word variations have been searched)

#13 Sympathetic dystrophy syndrome:ti,ab,kw (Word variations have been searched)

#14 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13

#15 MeSH descriptor: [Physical Therapy Modalities] explode all trees

#16 physiotherap*:ti,ab,kw (Word variations have been searched)

#17 "physical therap*":ti,ab,kw (Word variations have been searched)

#18 manual therapy:ti,ab,kw (Word variations have been searched)

#19 manipulative therapy:ti,ab,kw (Word variations have been searched)

#20 ((therapeutic or therapy) near/2 exercise):ti,ab,kw (Word variations have been searched)

#21 MeSH descriptor: [Electric Stimulation Therapy] explode all trees

#22 (electrotherapy or TENS or "transcutaneous electrical nerve stimulation" or "therapeutic ultrasound" or interferential or "shortwave diathermy" or "laser therapy " or "heat therapy" or cryotherapy):ti,ab,kw (Word variations have been searched)

#23 graded motor imagery:ti,ab,kw (Word variations have been searched)

#24 mirror therapy:ti,ab,kw (Word variations have been searched)

#25 MeSH descriptor: [Musculoskeletal Manipulations] explode all trees

#26 tactile sensory discriminatory training:ti,ab,kw (Word variations have been searched)

#27 sensory-motor integration:ti,ab,kw (Word variations have been searched)

#28 sensory-motor re-tuning:ti,ab,kw (Word variations have been searched)

#29 hydrotherapy:ti,ab,kw (Word variations have been searched)

#30 (pain near/3 (advice or education)):ti,ab,kw (Word variations have been searched)

#31 (manipulation or massage or de-sensiti?ation or mobili?ation):ti,ab,kw (Word variations have been searched)

#32 #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31

#33 #14 and #32

MEDLINE search strategy

1. exp Complex Regional Pain Syndromes/

2. "complex regional pain syndrome*".tw.

3. crps.tw.

4. (Post traumatic adj1 (algodystrophy or dystrophy or neurodystrophy or osteoporosis or pain syndrome)).tw.

5. "Minor causalgia".tw.

6. "Transient migratory osteoporosis".tw.

7. "Peripheral trophneurosis".tw.

8. "Sudeck's Osteodystrophy".tw.

9. "Neurovascular dystrophy".tw.

10. ((Major or mitchell*) adj1 causalgia).tw.

11. Sympathalgia.tw.

12. Chronic traumatic oedema.tw.

13. Sympathetic dystrophy syndrome.tw.

14. or/1-13

15. exp Physical Therapy Modalities/

16. physiotherap*.tw.

17. "physical therap*".tw.

18. manual therapy.tw.

19. manipulative therapy.tw.

20. ((therapeutic or therapy) adj2 exercise).tw.

21. exp Electric Stimulation Therapy/

22. (electrotherapy or TENS or "transcutaneous electrical nerve stimulation" or "therapeutic ultrasound" or interferential or "shortwave diathermy" or "laser therapy " or "heat therapy" or cryotherapy).tw.

23. graded motor imagery.tw.

24. mirror therapy.tw.

25. exp Musculoskeletal Manipulations/

26. tactile sensory discriminatory training.tw.

27. sensory-motor integration.tw.

28. sensory-motor re-tuning.tw.

29. hydrotherapy.tw.

30. (pain adj3 (advice or education)).tw.

31. (manipulation or massage or de-sensiti#ation or mobili#ation).tw.

32. or/15-31

33. 14 and 32

34 randomized controlled trial.pt.

35 controlled clinical trial.pt.

36 randomized.ab.

37 placebo.ab.

38 drug therapy.fs.

39 randomly.ab.

40 trial.ab.

41 or/34-40

42 exp animals/ not humans.sh.

43 41 not 42

44 33 and 43

Embase search strategy

1. exp Complex Regional Pain Syndromes/

2. "complex regional pain syndrome*".tw.

3. crps.tw.

4. (Post traumatic adj1 (algodystrophy or dystrophy or neurodystrophy or osteoporosis or pain syndrome)).tw.

5. "Minor causalgia".tw.

6. "Transient migratory osteoporosis".tw.

7. "Peripheral trophneurosis".tw.

8. "Sudeck's Osteodystrophy".tw.

9. "Neurovascular dystrophy".tw.

10. ((Major or mitchell*) adj1 causalgia).tw.

11. Sympathalgia.tw.

12. Chronic traumatic oedema.tw.

13. Sympathetic dystrophy syndrome.tw.

14. or/1-13

15. exp Physical Therapy Modalities/

16. physiotherap*.tw.

17. "physical therap*".tw.

18. manual therapy.tw.

19. manipulative therapy.tw.

20. ((therapeutic or therapy) adj2 exercise).tw.

21. exp Electric Stimulation Therapy/

22. (electrotherapy or TENS or "transcutaneous electrical nerve stimulation" or "therapeutic ultrasound" or interferential or "shortwave diathermy" or "laser therapy " or "heat therapy" or cryotherapy).tw.

23. graded motor imagery.tw.

24. mirror therapy.tw.

25. exp Musculoskeletal Manipulations/

26. tactile sensory discriminatory training.tw.

27. sensory-motor integration.tw.

28. sensory-motor re-tuning.tw.

29. hydrotherapy.tw.

30. (pain adj3 (advice or education)).tw.

31. (manipulation or massage or de-sensiti#ation or mobili#ation).tw.

32. or/15-31

33. 14 and 32

34 random$.tw.

35 factorial$.tw.

36 crossover$.tw.

37 cross over$.tw.

38 cross-over$.tw.

39 placebo$.tw.

40 (doubl$ adj blind$).tw.

41 (singl$ adj blind$).tw.

42 assign$.tw.

43 allocat$.tw.

44 volunteer$.tw.

45 Crossover Procedure/

46 double-blind procedure.tw.

47 Randomized Controlled Trial/

48 Single Blind Procedure/

49 or/34-48 (1433702)

50 (animal/ or nonhuman/) not human/

51 49 not 50

52 33 and 51

PsycINFO search strategy

1. exp "Complex Regional Pain Syndrome (Type I)"/

2. "complex regional pain syndrome*".tw.

3. crps.tw.

4. (Post traumatic adj1 (algodystrophy or dystrophy or neurodystrophy or osteoporosis or pain syndrome)).tw.

5. "Minor causalgia".tw.

6. "Transient migratory osteoporosis".tw.

7. "Peripheral trophneurosis".tw.

8. "Sudeck's Osteodystrophy".tw.

9. "Neurovascular dystrophy".tw.

10. ((Major or mitchell*) adj1 causalgia).tw.

11. Sympathalgia.tw.

12. Chronic traumatic oedema.tw.

13. Sympathetic dystrophy syndrome.tw.

14. or/1-13

15. exp Physical Therapy/

16. physiotherap*.tw.

17. "physical therap*".tw.

18. manual therapy.tw.

19. manipulative therapy.tw.

20. ((therapeutic or therapy) adj2 exercise).tw.

21. exp Electrical Stimulation/

22. (electrotherapy or TENS or "transcutaneous electrical nerve stimulation" or "therapeutic ultrasound" or interferential or "shortwave diathermy" or "laser therapy " or "heat therapy" or cryotherapy).tw.

23. graded motor imagery.tw.

24. mirror therapy.tw.

25. tactile sensory discriminatory training.tw.

26. sensory-motor integration.tw.

27. sensory-motor re-tuning.tw.

28. hydrotherapy.tw.

29. (pain adj3 (advice or education)).tw.

30. (manipulation or massage or de-sensiti#ation or mobili#ation).tw.

31. or/15-30

32. 14 and 31

33. clinical trials/

34. (randomis* or randomiz*).tw.

35. (random$ adj3 (allocat$ or assign$)).tw.

36. ((clinic$ or control$) adj trial$).tw.

37. ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).tw.

38. (crossover$ or "cross over$").tw.

39. random sampling/

40. Experiment Controls/

41. Placebo/

42. placebo$.tw.

43. exp program evaluation/

44. treatment effectiveness evaluation/

45. ((effectiveness or evaluat$) adj3 (stud$ or research$)).tw.

46. or/33-45

47. 32 and 46

CINAHL search strategy

S43 S33 AND S42

S42 S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41

S41 (allocat* random*)

S40 (MH "Quantitative Studies")

S39 (MH "Placebos")

S38 placebo*

S37 (random* allocat*)

S36 (MH "Random Assignment")

S35 (Randomi?ed control* trial*)

S34 (singl* blind*) or (doubl* blind*) or (tripl* blind*) or (trebl* blind*) or (trebl* mask*) or (tripl* mask*) or

(doubl* mask*) or (singl* mask*)

S33 S14 AND S32

S32 S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31

S31 (manipulation or massage or de-sensiti?ation or mobili?ation)

S30 (pain N3 (advice or education))

S29 hydrotherapy

S28 sensory-motor re-tuning

S27 sensory-motor integration

S26 tactile sensory discriminatory training

S25 (MH "Manual Therapy+")

S24 mirror therapy

S23 graded motor imagery

S22 (electrotherapy or TENS or "transcutaneous electrical nerve stimulation" or "therapeutic ultrasound" or interferential or "shortwave diathermy" or "laser therapy " or "heat therapy" or cryotherapy)

S21 (MH "Transcutaneous Electrical Nerve Stimulation (Iowa NIC)")

S20 ((therapeutic or therapy) N2 exercise)

S19 manipulative therapy

S18 manual therapy

S17 "physical therap*"

S16 physiotherap*

S15 (MH "Physical Therapy+")

S14 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13

S13 Sympathetic dystrophy syndrome

S12 Chronic traumatic oedema

S11 Sympathalgia

S10 ((Major or mitchell*) N1 causalgia)

S9 "Neurovascular dystrophy"

S8 "Sudeck's Osteodystrophy"

S7 "Peripheral trophneurosis"

S6 "Transient migratory osteoporosis"

S5 "Minor causalgia"

S4 (Post traumatic N1 (algodystrophy or dystrophy or neurodystrophy or osteoporosis or pain syndrome))

S3 crps

S2 "complex regional pain syndrome*"

S1 (MH "Complex Regional Pain Syndromes+")

LILACS search strategy

1. "crps"

2. "physiotherapy"

3. "clinical trial"

PEDro search strategy

1. "complex regional pain syndrome"

2. "reflex sympathetic dystrophy"

3. "causalgia"

4. "sudeks'"

5. "sympathetic pain"

6. "clinical trial"

Web of Science search strategy

1. "crps"

2. "physiotherapy"

3. "orthopaedic rehabilitation"

4. "articles"

Appendix 2. Update search strategies (February 2015 to July 2020)

CENTRAL search strategy

#1 MeSH descriptor: [Complex Regional Pain Syndromes] explode all trees

#2 "complex regional pain syndrome*":ti,ab,kw (Word variations have been searched)

#3 crps:ti,ab,kw (Word variations have been searched)

#4 (Posttraumatic near/1 (algodystrophy or dystrophy or neurodystrophy or osteoporosis or pain syndrome)):ti,ab,kw (Word variations have been searched)

#5 "Minor causalgia":ti,ab,kw (Word variations have been searched)

#6 "Transient migratory osteoporosis":ti,ab,kw (Word variations have been searched)

#7 "Peripheral trophneurosis":ti,ab,kw (Word variations have been searched)

#8 ((Major or mitchell*) near/1 causalgia):ti,ab,kw (Word variations have been searched)

#9 "Neurovascular dystrophy":ti,ab,kw (Word variations have been searched)

#10 "Sudecks Osteodystrophy":ti,ab,kw (Word variations have been searched)

#11 Sympathalgia:ti,ab,kw (Word variations have been searched)

#12 Chronic traumatic oedema:ti,ab,kw (Word variations have been searched)

#13 Sympathetic dystrophy syndrome:ti,ab,kw (Word variations have been searched)

#14 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13

#15 MeSH descriptor: [Physical Therapy Modalities] explode all trees

#16 physiotherap*:ti,ab,kw (Word variations have been searched)

#17 "physical therap*":ti,ab,kw (Word variations have been searched)

#18 manual therapy:ti,ab,kw (Word variations have been searched)

#19 manipulative therapy:ti,ab,kw (Word variations have been searched)

#20 ((therapeutic or therapy) near/2 exercise):ti,ab,kw (Word variations have been searched)

#21 MeSH descriptor: [Electric Stimulation Therapy] explode all trees

#22 (electrotherapy or TENS or "transcutaneous electrical nerve stimulation" or "therapeutic ultrasound" or interferential or "shortwave diathermy" or "laser therapy" or "heat therapy" or cryotherapy):ti,ab,kw (Word variations have been searched)

#23 graded motor imagery:ti,ab,kw (Word variations have been searched)

#24 mirror therapy:ti,ab,kw (Word variations have been searched)

#25 MeSH descriptor: [Musculoskeletal Manipulations] explode all trees

#26 tactile sensory discriminatory training:ti,ab,kw (Word variations have been searched)

#27 sensory-motor integration:ti,ab,kw (Word variations have been searched)

#28 sensory-motor re-tuning:ti,ab,kw (Word variations have been searched)

#29 hydrotherapy:ti,ab,kw (Word variations have been searched)

#30 (pain near/3 (advice or education)):ti,ab,kw (Word variations have been searched)

#31 (manipulation or massage or de-sensiti?ation or mobili?ation):ti,ab,kw (Word variations have been searched)

#32 MeSH descriptor: [Implosive Therapy] explode all trees

#33 ("Bio-Electro-Magnetic-Energy-Regulation"):ti,ab,kw (Word variations have been searched)

#34 (neuromuscular electrical stimulation):ti,ab,kw (Word variations have been searched)

#35 (Electromagnetic Field Therapy):ti,ab,kw (Word variations have been searched)

#36 (Virtual body swapping):ti,ab,kw (Word variations have been searched)

#37 ("Action observation"):ti,ab,kw (Word variations have been searched)

#38 (Mental visuali*ation):ti,ab,kw (Word variations have been searched)

#39 ("Pain-contingent treatment*"):ti,ab,kw (Word variations have been searched)

#40 MeSH descriptor: [Transcranial Direct Current Stimulation] this term only

#41 (Transcranial direct current stimulation):ti,ab,kw (Word variations have been searched)

#42 MeSH descriptor: [Desensitization, Psychologic] explode all trees

#43 (Desensiti*ation):ti,ab,kw (Word variations have been searched)

#44 #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43

#45 #14 and #44 with Cochrane Library publication date Between Feb 2015 and Jul 2020, in Trials

MEDLINE and MEDLINE in process search strategies

1 exp Complex Regional Pain Syndromes/ (5534)

2 "complex regional pain syndrome*".tw. (2996)

3 crps.tw. (2313)

4 (Post traumatic adj1 (algodystrophy or dystrophy or neurodystrophy or osteoporosis or pain syndrome)).tw. (51)

5 "Minor causalgia".tw. (8)

6 "Transient migratory osteoporosis".tw. (7)

7 "Peripheral trophneurosis".tw. (0)

8 "Sudeck's Osteodystrophy".tw. (7)

9 "Neurovascular dystrophy".tw. (25)

10 ((Major or mitchell*) adj1 causalgia).tw. (6)

11 Sympathalgia.tw. (17)

12 Chronic traumatic oedema.tw. (0)

13 Sympathetic dystrophy syndrome.tw. (223)

14 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 (7267)

15 exp Physical Therapy Modalities/ (152617)

16 physiotherap*.tw. (25431)

17 "physical therap*".tw. (22290)

18 manual therapy.tw. (2024)

19 manipulative therapy.tw. (831)

20 ((therapeutic or therapy) adj2 exercise).tw. (5752)

21 exp Electric Stimulation Therapy/ (79793)

22 (electrotherapy or TENS or "transcutaneous electrical nerve stimulation" or "therapeutic ultrasound" or interferential or "shortwave diathermy" or "laser therapy " or "heat therapy" or cryotherapy).tw. (34642)

23 graded motor imagery.tw. (53)

24 mirror therapy.tw. (339)

25 exp Musculoskeletal Manipulations/ (16656)

26 tactile sensory discriminatory training.tw. (0)

27 sensory-motor integration.tw. (295)

28 sensory-motor re-tuning.tw. (0)

29 hydrotherapy.tw. (958)

30 (pain adj3 (advice or education)).tw. (1707)

31 (manipulation or massage or de-sensiti#ation or mobili#ation).tw. (159532)

32 exp Implosive Therapy/ (1277)

33 "Bio-Electro-Magnetic-Energy-Regulation".tw. (5)

34 neuromuscular electrical stimulation.tw. (1220)

35 Electromagnetic Field Therapy.tw. (136)

36 Virtual body swapping.tw. (3)

37 "Action observation".tw. (1169)

38 Mental visuali#ation.tw. (32)

39 "Pain-contingent treatment*".tw. (2)

40 Transcranial Direct Current Stimulation/ (2610)

41 Transcranial direct current stimulation.tw. (4216)

42 exp Desensitization, Psychologic/ (3597)

43 Desensiti#ation.tw. (23332)

44 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 (443161)

45 14 and 44 (1120)

46 randomized controlled trial.pt. (509322)

47 controlled clinical trial.pt. (93750)

48 randomized.ab. (485366)

49 placebo.ab. (209221)

50 drug therapy.fs. (2218451)

51 randomly.ab. (336638)

52 trial.ab. (511833)

53 or/46-52 (3199899)

54 exp animals/ not humans.sh. (4715958)

55 53 not 54 (2864561)

56 45 and 55 (305)

57 (201502* or 201503* or 201504* or 201505* or 201506* or 201507* or 201508* or 201509* or 201510* or 201511* or 201512* or 2016* or 2017* or 2018* or 2019* or 2020*).ed. (5490256)

58 56 and 57 (92)

Embase search strategy

1 exp Complex Regional Pain Syndromes/ (8973)

2 "complex regional pain syndrome*".tw. (4356)

3 crps.tw. (3714)

4 (Post traumatic adj1 (algodystrophy or dystrophy or neurodystrophy or osteoporosis or pain syndrome)).tw. (40)

5 "Minor causalgia".tw. (5)

6 "Transient migratory osteoporosis".tw. (11)

7 "Peripheral trophneurosis".tw. (0)

8 "Sudeck's Osteodystrophy".tw. (4)

9 "Neurovascular dystrophy".tw. (18)

10 ((Major or mitchell*) adj1 causalgia).tw. (4)

11 Sympathalgia.tw. (9)

12 Chronic traumatic oedema.tw. (0)

13 Sympathetic dystrophy syndrome.tw. (260)

14 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 (10515)

15 exp Physical Therapy Modalities/ (83424)

16 physiotherap*.tw. (43543)

17 "physical therap*".tw. (32013)

18 manual therapy.tw. (2817)

19 manipulative therapy.tw. (868)

20 ((therapeutic or therapy) adj2 exercise).tw. (7641)

21 exp Electric Stimulation Therapy/ (229342)

22 (electrotherapy or TENS or "transcutaneous electrical nerve stimulation" or "therapeutic ultrasound" or interferential or "shortwave diathermy" or "laser therapy " or "heat therapy" or cryotherapy).tw. (41207)

23 graded motor imagery.tw. (86)

24 mirror therapy.tw. (559)

25 exp Musculoskeletal Manipulations/ (3181)

26 tactile sensory discriminatory training.tw. (0)

27 sensory-motor integration.tw. (383)

28 sensory-motor re-tuning.tw. (0)

29 hydrotherapy.tw. (1197)

30 (pain adj3 (advice or education)).tw. (2456)

31 (manipulation or massage or de-sensiti#ation or mobili#ation).tw. (190293)

32 exp Implosive Therapy/ (151)

33 "Bio-Electro-Magnetic-Energy-Regulation".tw. (8)

34 neuromuscular electrical stimulation.tw. (1585)

35 Electromagnetic Field Therapy.tw. (168)

36 Virtual body swapping.tw. (3)

37 "Action observation".tw. (1354)

38 Mental visuali#ation.tw. (41)

39 "Pain-contingent treatment*".tw. (3)

40 Transcranial Direct Current Stimulation/ (7038)

41 Transcranial direct current stimulation.tw. (6207)

42 exp Desensitization, Psychologic/ (76)

43 Desensiti#ation.tw. (28151)

44 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 (598234)

45 14 and 44 (2534)

46 random$.tw. (1533554)

47 factorial$.tw. (37636)

48 crossover$.tw. (74476)

49 cross over$.tw. (31451)

50 cross-over$.tw. (31451)

51 placebo$.tw. (303445)

52 (doubl$ adj blind$).tw. (203145)

53 (singl$ adj blind$).tw. (24789)

54 assign$.tw. (391068)

55 allocat$.tw. (152083)

56 volunteer$.tw. (250549)

57 Crossover Procedure/ (63463)

58 double-blind procedure.tw. (202)

59 Randomized Controlled Trial/ (605488)

60 Single Blind Procedure/ (39339)

61 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 (2296773)

62 (animal/ or nonhuman/) not human/ (5591375)

63 61 not 62 (2032509)

64 45 and 63 (317)

65 (201502* or 201503* or 201504* or 201505* or 201506* or 201507* or 201508* or 201509* or 201510* or 201511* or 201512* or 2016* or 2017* or 2018* or 2019* or 2020*).dd. (4258933)

66 64 and 65 (60)

PsycINFO search strategy

S55 S45 AND S53 Limiters - Publication Year: 2015-2020

S54 S45 AND S53

S53 S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52

S52 (singl* OR doubl* OR trebl* OR tripl*) N3 (blind* OR mask*)

S51 clinical N3 trial* OR research N3 design OR evaluat* N3 stud* OR prospectiv* N3 stud*

S50 placebo* OR random* OR "comparative stud*"

S49 DE "Followup Studies"

S48 DE "Placebo"

S47 DE "Treatment Outcomes" OR DE "Psychotherapeutic Outcomes" OR DE "Side Effects (Treatment)" OR DE "Treatment Compliance" OR DE "Treatment Duration" OR DE "Treatment Refusal" OR DE "Treatment Termination" OR DE "Treatment Withholding"

S46 DE "Treatment Effectiveness Evaluation"

S45 S14 AND S44

S44 S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43

S43 desensitization

S42 (MH "Desensitization, Psychologic+")

S41 Transcranial direct current stimulation

S40 (MH "Transcranial Direct Current Stimulation")

S39 "Pain-contingent treatment*"

S38 "Mental visuali?ation"

S37 "Action observation"

S36 "Virtual body swapping"

S35 "Electromagnetic Field Therapy"

S34 neuromuscular electrical stimulation

S33 "Bio-Electro-Magnetic-Energy-Regulation"

S32 (MH "Behavior Therapy+")

S31 (manipulation or massage or de-sensiti?ation or mobili?ation)

S30 (pain N3 (advice or education))

S29 hydrotherapy

S28 sensory-motor re-tuning

S27 sensory motor integration

S26 tactile sensory discriminatory training

S25 (MH "Manual Therapy+")

S24 mirror therapy

S23 graded motor imagery

S22 (electrotherapy or TENS or "transcutaneous electrical nerve stimulation" or "therapeutic ultrasound" or interferential or "shortwave diathermy" or "laser therapy " or "heat therapy" or cryotherapy)

S21 (MH "Transcutaneous Electrical Nerve Stimulation (Iowa NIC)")

S20 ((therapeutic or therapy) N2 exercise)

S19 manipulative therapy

S18 manual therapy

S17 "physical therap*"

S16 physiotherap*

S15 (MH "Physical Therapy+")

S14 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13

S13 Sympathetic dystrophy syndrome

S12 Chronic traumatic oedema

S11 Sympathalgia

S10 ((Major or mitchell*) N1 causalgia)

S9 "Neurovascular dystrophy"

S8 "Sudeck's Osteodystrophy"

S7 "Peripheral trophneurosis"

S6 "Transient migratory osteoporosis"

S5 "Minor causalgia"

S4 (Post traumatic N1 (algodystrophy or dystrophy or neurodystrophy or osteoporosis or pain syndrome))

S3 crps

S2 "complex regional pain syndrome*"

S1 (MH "Complex Regional Pain Syndromes+")

CINAHL search strategy

(+RCT filter)

S45 S14 AND S44

S44 S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43

S43 desensitization

S42 (MH "Desensitization, Psychologic+")

S41 Transcranial direct current stimulation

S40 (MH "Transcranial Direct Current Stimulation")

S39 "Pain-contingent treatment*"

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S37 "Action observation"

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S31 (manipulation or massage or de-sensiti?ation or mobili?ation)

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S29 hydrotherapy

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S20 ((therapeutic or therapy) N2 exercise)

S19 manipulative therapy

S18 manual therapy

S17 "physical therap*"

S16 physiotherap*

S15 (MH "Physical Therapy+")

S14 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13

S13 Sympathetic dystrophy syndrome

S12 Chronic traumatic oedema

S11 Sympathalgia

S10 ((Major or mitchell*) N1 causalgia)

S9 "Neurovascular dystrophy"

S8 "Sudeck's Osteodystrophy"

S7 "Peripheral trophneurosis"

S6 "Transient migratory osteoporosis"

S5 "Minor causalgia"

S4 (Post traumatic N1 (algodystrophy or dystrophy or neurodystrophy or osteoporosis or pain syndrome))

S3 crps

S2 "complex regional pain syndrome*"

S1 (MH "Complex Regional Pain Syndromes+")

PEDro search strategy

1. "complex regional pain syndrome"

2. "reflex sympathetic dystrophy"

3. "causalgia"

4. "sudeks'"

5. "sympathetic pain"

6. "clinical trial"

LILACS search strategy

1. “crps”

2. “physiotherapy”

3. “clinical trial”

Web of Science search strategy

1. "complex regional pain syndrome"

2. "articles"

3. "proceedings"

4. "randomized controlled trial"

WHAT'S NEW

Date	Event	Description
8 August 2022	Amended	Correction to the data reported for the comparison: Transcutaneous electrical nerve stimulation (TENS) versus sham TENS.

HISTORY

Protocol first published: Issue 11, 2013
Review first published: Issue 2, 2016

Date	Event	Description
27 September 2021	New citation required but conclusions have not changed	We have added 16 trials (600 participants) to this update. Our conclusions remain unchanged.
27 September 2021	New search has been performed	This review has been updated with the results of a new search in July 2021.
11 March 2016	Amended	Minor amendment to Analysis 1.2.

CONTRIBUTIONS OF AUTHORS

KMS conceived and designed the protocol, implemented the search strategy, applied eligibility criteria, assessed studies, extracted and analysed data, and led the write-up of the review.

MCF applied eligibility criteria, assessed studies, extracted and analysed data, and assisted with the write-up of the updated review.

BMW informed the protocol design, applied eligibility criteria, assessed studies, extracted and analysed data (in the original review), and assisted with the write-up of the review.

NOC informed the protocol design, acted as the third review author, oversaw data synthesis and assisted with the write-up of the review.

KMS will be responsible for updating this Cochrane Review.

DECLARATIONS OF INTEREST

KMS: none known. KMS maintains a small clinical caseload as a clinical specialist physiotherapist and manages patients with CRPS.

MCF: none known.

BMW: none known.

NOC: none known. NOC is an author as well as PaPaS Co-ordinating Editor but had no input into the editorial decisions or processes for this review.

KMS, BMW and NOC are qualified physiotherapists, and MCF is a health scientist, although none currently practice in private health care or for a 'for profit' organisation.

Since NOC is an author and PaPaS Co-ordinating Editor, we acknowledge the input of Christopher Eccleston, who acted as Sign-off Editor for this review. NOC had no input into the editorial decisions or processes for this review.

SOURCES OF SUPPORT

Internal sources

- No sources of support provided

External sources

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  Cochrane Infrastructure funding to the Cochrane Pain, Palliative and Supportive Care Review Group (PaPaS)

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

2016 Review

We did not search the reference lists of key physiotherapy textbooks. With respect to Types of interventions, after the publication of Smart 2013 we decided to exclude studies that evaluated non-physiotherapy based interventions (e.g. pharmacological) in which all study arms received the same physiotherapy intervention (differing only in the application of the non-physiotherapy component) as they are unlikely to offer any insight into the value of physiotherapy management. In Smart 2013 we stated our intention to search the SciVerse SCOPUS electronic database. However, we did not search this database as the primary review author (KMS) did not have institutional access. The Information Specialist of the Cochrane PaPaS group advised that its omission was unlikely to adversely influence our search results. We have described, in additional detail, our operational definitions upon which we based our risk of bias judgements (see the Assessment of risk of bias in included studies section). In the original Cochrane Review we specified the criteria upon which we based our GRADE judgements for rating the quality of evidence (see the Data synthesis section).

2021 Update

In a change to our original protocol (Smart 2013) and systematic review (Smart 2016) we extended our interpretation of changes in outcomes to include between-group differences based on the recommendations of the OMERACT 12 group, as detailed in the Primary outcomes section. In a further change we also excluded studies that did not measure any of the primary or secondary outcomes of interest. Our GRADE judgements now rate the 'certainty' rather then the 'quality' of evidence (see 'Summary of findings and assessment of the certainty of the evidence' section). We have explained and justified our presentation of a limited number of summary of findings tables in the summary of findings table section.

INDEX TERMS

Medical Subject Headings (MeSH)

*Complex Regional Pain Syndromes [therapy]; *Electric Stimulation Therapy; Pain; Pain Measurement; Physical Therapy Modalities

MeSH check words

Adult; Humans